ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

The problem of publishing annually a volume of standard size purporting to review the current developments in physiology, when these are expanding in geometric progression, is one requiring continuous adaptation. The latest phase of this adaptation has taken two forms.

Firstly, the Editorial Committee has in recent years earnestly pleaded with our reviewers to consider only those papers which they deem particularly noteworthy contributions to our science and to reduce coverage of other papers to mere listing. It was hoped that, without impairing the usefulness of the *Review* as an index to all pertinent contributions, critical appraisal of outstanding advances would receive greater emphasis. We feel that a significant improvement of the quality of the reviews has followed the adoption of this policy.

Secondly, the scope of the *Review* has been more nearly confined to the domain of classical physiology by the omission of certain types of chapters, with corresponding increases in the space devoted to the conventional subdivisions of physiology. The chapters on applied physiology in its various aspects (exercise, anoxia and the like) will be discontinued. The announcement of the appearance in 1950 of several new publications by Annual Reviews, Inc., will give us some relief. The *Annual Review of Psychology* will make unnecessary the chapter on physiological psychology. The *Annual Review of Medicine* will relieve us of chapters on topics in pathology. The *Annual Review of Plant Physiology* and the *Annual Review of Physical Chemistry* will contain material of interest to readers of this series.

This reduction in the number of chapters is, however, not intended in any sense as a renunciation of the role of physiology as a co-ordinator and interpreter of natural phenomena exhibited by living organisms in health and illness, under usual and unusual conditions. Accordingly, contributions made to physiological problems by means of pharmacological, pathological, and psychological techniques will be considered in the chapters devoted to the aspect of physiology to which they are related.

In this connection it is pertinent to recognize the increasing volume and quality of fundamental research being carried out in

laboratories of clinical medicine, surgery, and pathology, which is enriching physiology as well as aiding the practice of medicine. It is equally pertinent to assert the claim of physiology to a growing place in the medical curriculum. We note with approval the extension of physiological instruction into the later years of some of our medical schools. Similarly, as engineers continually devise new machines placing stresses on the human organism beyond any previous experience, the study of the resulting problems is enlarging the scope of physiology. The inclusion in the engineering curriculum of courses in which the physiological limitations of man are considered as factors in design is a logical result of this development, with undoubted potential mutual benefit to both fields.

Two chapters announced for this volume are missing. That on the Physiological Effects of Heat and Cold was to have been written by Dr. H. O. Haterius, whose untimely death has deprived this aspect of physiology of one of its most active workers. The section on Cutaneous Sensation which was promised several years ago by Assistant Commissar N. Propper-Graschenkov did not reach us, no reply to our repeated inquiries having been received through the devious channels of officialdom which separate us from our Russian colleagues.

We announce with sincere regret the retirement for reasons of health from the Editorial Committee of Dr. Walter J. Meek, who was largely instrumental in conducting the negotiations whereby the American Physiological Society joined forces with Annual Review of Biochemistry, Ltd., to initiate publication of the *Annual Review of Physiology*, and who served as Chairman of the Board during the formative years of the *Review*. In his place we welcome Dr. Maurice Visscher of the University of Minnesota, who is also President of the American Physiological Society.

A *Cumulative Index* to the first ten volumes of the *Annual Review of Physiology* will make its appearance during this year. It will index by subjects and authors that portion of the physiological literature appearing during the period of approximately 1938 to 1947 which has been deemed by our various reviewers to merit mention. As the sole index in physiology covering more than one year in a single volume, it should be of great value to workers in our field.

It is with a feeling that their loyal and painstaking labors are

never properly appreciated that we thank our editorial and secretarial assistants, Ruth Swan, Virginia Lee, Barbara Darneal, Barbara Davey, Dorothy Bauck, Cornelius Cotter, Beatrice Schlamp, and Faith Lentz, for their part in the preparation of this volume. Dr. J. Murray Luck, virtual founder and first Editor, continues his indispensable services as director of the financial and administrative aspect of the *Review*. To our printers, The George Banta Publishing Company, we again extend our appreciation for their cordial collaboration.

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CONTENTS

	PAGE
DEVELOPMENTAL PHYSIOLOGY, *A. M. Schechtman*	1
REPRODUCTION, *H. R. Catchpole*	21
METABOLIC FUNCTIONS OF THE ENDOCRINE SYSTEM, *S. B. Barker*	45
LIVER, *F. W. Hoffbauer*	83
DIGESTIVE SYSTEM, *J. E. Thomas and M. H. F. Friedman*	103
VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM, *W. B. Youmans*	139
SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM, *H. W. Magoun*	161
BIOELECTRIC POTENTIALS IN THE NERVOUS SYSTEM AND MUSCLE, *D. P. C. Lloyd and A. K. McIntyre*	173
THE ELECTRICAL ACTIVITY OF THE BRAIN, *W. G. Walter and V. J. Walter*	199
HEARING, *E. M. Walzl*	231
VISION, *S. A. Talbot*	245
PHYSIOLOGICAL PSYCHOLOGY, *H. F. Harlow*	269
MUSCLE, *A. Sandow*	297
HEMATOPOIESIS, *G. E. Cartwright and M. M. Wintrobe*	335
THE LYMPHATIC SYSTEM, *A. White*	355
HEART, *J. S. Robb*	387
PERIPHERAL CIRCULATION, *E. Ogden and C. E. Hall*	435
RESPIRATION, *O. A. M. Wyss*	469
KIDNEY, *R. A. Phillips*	493
RADIATION, *L. F. Nims*	527
PERMEABILITY, *T. Teorell*	545
PHARMACOLOGY, *G. K. Moe and F. E. Shideman*	565
INDEXES	587

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DEVELOPMENTAL PHYSIOLOGY

By A. Mandel Schechtman

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The present review is concerned mainly with change—the physiology of embryonic differentiation—rather than with functions more obviously of an operational nature. The writer is conscious of the difficulties involved in the assumption that embryonic functions can, in the first place, be segregated into categories of differentiation versus operation. However space limitations have compelled selection, and such topics as mechanics of heart action, transport of gases, fetal muscular activity, and function of the nervous system have been left for future reviews.

Fertilization.—Following up his earlier work on the cytolytic action of lecithinase, Öhman (1) has obtained data which indicate a decrease in the phosphatide content of the surface of the sea urchin egg as a result of fertilization. A decrease in susceptibility to cytolysis occurs shortly after fertilization, followed by a second period of increased susceptibility, and again a third period of decreased susceptibility, this last period coinciding with the time when the egg is preparing for cleavage. One may only speculate on the possible relation between these findings and the shift in alkaline phosphatase as shown by the Gomori method (2). In young oocytes of the sea urchin alkaline phosphatase is concentrated in the nucleolus and nuclear membrane, whereas in the mature egg it occurs in granules of the cortex and after fertilization is quite evenly distributed through the cytoplasm.

Monroy & Montalenti (3) have related birefringence or its absence in the cortex of the sea urchin egg to the type of cellular shrinkage produced by hypertonic sea water. Uniform shrinkage (spherical plasmolysis) corresponds with the period of cortical birefringence, whereas irregular shrinkage (angular plasmolysis) corresponds with lack of birefringence. The interpretation is that radially oriented micelles characterize the cortex of the unfertilized egg, whereas a disorderly pattern occurs after fertilization. Monroy (4) suggests that the cortex contains a lipid-protein complex with the lipids arranged radially. Brooks (5), from a study of the activation of eggs by various redox dyes, finds marked agreement

between the rH values of the most effective dyes and of homologous sperm. This supports the suggestion previously made by the author that activation depends upon the establishment of appropriate redox potential. Cheney (14), from studies on caffeine inhibition of oxygen uptake in *Arbacia*, finds that fertilization is independent of a respiratory mechanism required shortly afterward. Barron *et al.* (132) have shown a similar difference in respiratory mechanism by the use of nitrogen mustards.

The "myosin-like" protein obtained by Mirsky (134) from sea urchin eggs was found by Connors & Scheer (6) to be completely lacking in adenosinetriphosphatase activity, whether obtained from fertilized or unfertilized eggs. Substances which liberate phosphate are present and apparently increase on fertilization, but cannot be accounted for by Mirsky's protein nor by a small amount of alkaline phosphatase activity. In electrophoresis only a single component appears.

The source of hyaluronidase and its role in fertilization were investigated by several groups with results in essential agreement (7 to 12). Three fourths of the hyaluronidase activity of rabbit semen is in the washed sperm which liberate the enzyme into aqueous solution (7, 9). In man, rabbit, bull, and boar the hyaluronidase content is in close correlation with sperm density. However, this does not hold true for the fowl and dog. The enzyme is lacking in cryptorchids and prepubertal rabbits (8). However, aspermic specimens of semen contain the spreading factor, which is evidently present in relatively low concentration since such aspermic specimens did not reduce the viscosity of hyaluronic acid solutions (10). Conditions which decrease sperm motility or are obviously injurious to the sperm increase the content of free enzyme (11).

The role of hyaluronidase as a disperser of follicle cells is supported by Swyer (12), who was unable to demonstrate the enzyme in the testes of reptiles or, except in negligible amounts, in fowl semen. Since the ova of these forms are not coated with follicle cells, hyaluronidase would appear to be superfluous. Leonard *et al.* (13) made the surprising observation that rat sperm penetrate ova before dispersal of the cumulus by hyaluronidase action. The authors suggest that the enzyme may, nevertheless, aid the sperm in penetrating between the follicle cells. Uterine fluid was found to denude the ova rather rapidly *in vitro*.

Of technical interest are a simple method for obtaining rat eggs

(16) and the finding that rabbit ova can be maintained in viable condition for as long as 168 hours if stored in rabbit serum at 10°C. (17).

Genes and developmental processes.—A number of valuable contributions to the general theory of differentiation have appeared (18 to 26). Huskins (18, 19) reconsiders the concept still generally accepted that all the somatic cells of an organism possess the same genic constitution. Several recent studies of chromosome banding suggest differences between various tissues, but Huskins thinks heterochromatic variations are probably too crude to provide a basis for gene action. Variations in the number of strands composing the supposed unitary chromatid are reported. If the rates of reproduction of various chromatids were variable, such quantitative differences would appear. The occurrence of various degrees of endopolyploidy in differentiated tissues of insects and plants supports the assumption that differentiation may involve quantitative nuclear variations. Prokofyeva-Belgovskaya (20) suggests that the degree of heterochromaticity may modify developmental processes in different cells, development varying with the type of genic function obliterated. Schultz (21) also emphasizes heterochromaticity in an interesting hypothesis of "genic adaptation." In the various tissues relatively few of the genes remain "active" in specific syntheses, most of them becoming concerned with over-all nucleoprotein metabolism. In differentiation an irreversible genic pattern is established by the development of a semi-autonomous cytoplasmic system associated with ribose-nucleoproteins. Spiegelman (22) discusses the recent work on adaptive enzyme formation with relation to differentiation. The presence of specific substrates would stabilize homologous enzymes against decay. Since enzyme formation is under gene control, it seems possible that the substrate would accentuate the capacity of genes to produce certain enzymes. Thus the same genes might exist potentially in all nuclei, but with varying activity. Monod (23) has developed a similar line of thought but suggests an orderly selection of spontaneous gene mutations under the local conditions prevailing in various cells. Sonneborn (24) suggests that the cytoplasm of the egg may contain self-duplicating units, in principle like the kappa factor in *Paramecium*. If it be supposed that such factors multiply at varying rates, some of them so slowly that they fall behind cell division, we would eventually have a diversified cell

population. Several other possible differentiation mechanisms are suggested. By the use of desoxyribonuclease and proteolytic enzymes, van Wagtendonk (25) has found that the killer substance of *Paramecium* is desoxyribonucleoprotein. It seems worth while keeping in mind the possible role of small amounts of cytoplasmic desoxyribonucleoprotein specific syntheses in higher organisms. Desoxyribonucleic acid is discharged from resting, vegetative nuclei into the cytoplasm but retained in generative nuclei [Huskins (19)]; and the transforming agents of pneumococci and other bacteria are apparently desoxyribonucleic acids, effective in exceedingly minute amounts. Brachet (26) suggests that the cytoplasmic particles containing ribonucleic acid may increase in complexity during development and lead to the synthesis of specific kinds of protein. In the same paper (26) the relationships between nuclear and cytoplasmic nucleic acids are discussed.

Strong (27), continuing his work on methylcholanthrene as a mutagenic and teratogenic agent, reports hereditary dwarfism which seems almost certainly to be due to methylcholanthrene. The relation of heterochromatin to ribonucleic acid content was studied by Callan (28), who was unable to show any differences in ribonucleic acid concentration in XX and XXY *Drosophila* eggs. Villee (29) finds that the genes for miniature and vestigial wing markedly decrease the oxygen uptake of the wing discs. The genes exert their depressing effect locally, in the wing rudiment, for no such effect could be observed in leg rudiments. Respiration is probably mediated by cytochrome-cytochrome oxidase, with the mutant genes producing their effects below cytochrome-*c*.

Briggs (30) obtained normal triploid tadpoles by heating *Rana pipiens* eggs at 37°C. shortly after insemination. Growth and development are essentially as in diploids, but the cells are 50 per cent larger. The depression in mitotic rate, which must occur, probably takes effect in the late blastula or gastrula. Moore (31, 32) obtained defective embryos by fertilizing *Rana pipiens* eggs with *Rana sylvatica* sperm. Moore finds that the arrest in development, which occurs at the end of the blastula stage, is more than a mere block of the gastrulation movements. The ectoderm of the hybrids is less competent to carry out various differentiations (31) and the dorsal lips of hybrids are poor inductors. Thus, in both Briggs's and Moore's studies, as in a number of previous studies, the defects produced by nuclear abnormalities are expressed at that period in

development when synthesis of total nucleic acids gets under way. The subject is discussed in some detail by Brachet (26).

Environmental modifications of development.—Recent works on the effects of vitamin deficiency and metabolic inhibitors suggest wide fields for investigations of the metabolism of the embryo. The organism is, of course, at all times a function of the variables in its internal environment, and we have only very incomplete knowledge of how these variables affect the structure and function of organisms in early stages of their life cycles.

Warkany & Roth (33) find a variety of abnormalities in rat embryos from mothers fed a diet deficient in vitamin A—retrolenticular membranes, absence of vitreous humor in the eye, the failure of the pleural chambers to extend ventrolaterally around the pericardial coelom, the testes undescended, etc. The deficiencies are quite distinct from those induced by maternal riboflavin deficiency. The results suggest that the early morphogenetic processes require lower concentrations of the vitamin than the later stages. Hainsborough (34) tried to create a vitamin imbalance in the vitamin-rich environment of the chick embryo by carotene and vitamin A and D injections under the vitelline membrane. Comparing experimental animals with oil-injected controls, it is concluded that abnormalities, especially of the vascular system, may be attributed to the vitamin excess. In older chick embryos Branson *et al.* (46) obtained an acceleration in over-all phosphorus metabolism after injection of vitamin D. Hainsborough (37) also finds that injection of nicotinic acid inhibits the closure of the neural plate, the invagination of the optic vesicle, and formation of the normal heart curvature. Strong & Hollander (35) think it probable that the lethal effects on embryos, produced by intraperitoneal injection of methylcholanthrene into the mother, are mediated through a vitamin A deficiency. A high maternal cholesterol diet reduces the vitamin A content in the fetus (79), but the reduction apparently is insufficient to produce abnormalities.

Pantothenic acid deficiency produces no characteristic developmental deficiencies *in ovo* although the chicks seem to lack the energy to break out of the shell [Gillis *et al.* (36)].

Couch *et al.* (38, 39) produced a biotin deficiency in the egg by feeding hens sucrose or sucrose plus lactose as the carbohydrate source. There was a high incidence of skeletal abnormalities (micromelia, syndactyly), perosis, and ataxia. It is suggested that the

skeletal defects are possibly mediated through effects on the musculature.

Landauer (40) in a continuation of his work on insulin-induced skeletal abnormalities in the chicken finds that certain embryonic stages are more susceptible to production of such specific defects as rumplessness, short legs, and protruding eyes. The defects appear to be phenocopies of mutants studied earlier. Moseley (42), in a study of the early embryology of insulin-injected embryos, finds abnormal developmental processes similar to those occurring in the recessive type of rumplessness. Zwilling (43) injected insulin into thirty-hour and five-day-old chick embryos and found that their metabolism is already insulin-sensitive as shown by the development of persistent hypoglycemia. As far as is known the hormones of the pituitary, adrenal cortex, and islets of Langerhans, all involved in insulin activity in the adult, are not elaborated by the chick during this early period. Since insulin is known to stimulate the adrenal cortex, and insulin hypoglycemia increases endogenous epinephrine, it is of interest that Landauer (44) was unable to induce the abnormalities previously mentioned either with extract of the adrenal cortex or with epinephrine. Insulin deficiency also produces profound effects on the mammalian fetus. When female rats are made diabetic by alloxan during the early part of gestation, the embryos die in midpregnancy [Davis *et al.* (45)]. Earlier work had indicated that insulin had little effect in advanced pregnancy suggesting that perhaps the early stages are more sensitive.

Thyroid inhibitors were tested on the chick at the eighth and fourteenth day of incubation (47), and on the larvae of a toad which never develops gills, suckers, or horny teeth (48). In both instances there was evidence of hyperplasia and hypofunction of the thyroid. In the case of the toad larvae it was apparent that precocious thyroid function probably does not account for the absence of the larval features in the species studied.

Mandel *et al.* (49) find that testosterone decreases the total weight and lipid content of the brain of the chick embryo, and Meyer *et al.* (50) obtained severe exogastrulation and spina bifida in frog embryos with estrogens. Again the gastrula appears as a crucial stage since many of the embryos never develop beyond the blastula. On the other hand Gabrio & Salomon (130) find that the

calcifying mechanism of the chick, in contrast to that of the adult, is insensitive to estradiol.

Rostand (51, 52) produced the diploid condition in haploid anurans by subjecting them to 0°C. shortly after activation. Hsu (53) found a remarkable heat-susceptibility in rat embryos. When the body temperature of the mother was raised between 2° and 3°C. above normal, developmental stages up to the time of implantation were killed, while postimplantation stages were resistant. Detwiler *et al.* (54) tested sulfadiazine and quinine sulfate on urodele embryos and found the drugs useful, in concentrations of 0.5 per cent and 1 mg. per ml. respectively, for the maintenance of operated specimens. The effects of metrazol on various stages of *Fundulus* was reported by Oppenheimer (109). The morphogenetic effects of thiocyanate and lithium chloride on development may be related to the observation by Ranzi (55) that thiocyanate causes a loss of fibrillar structure in rabbit myosin in potassium chloride solution, whereas lithium chloride accentuates fibrillar structure. Wolff & Lutz (56) produced twinning in duck embryos by cutting through the blastoderm, and Wolff & Kahn (57) produced duplications of the wings and legs of chick embryos in the twenty to thirty somite stage by splitting the limb anlage or the early limb bud prior to the palette stage.

Hamburger & Habel (58) showed that influenza A, like rubella, is strongly teratogenic in the chick, with a tendency to attack the brain rather than the respiratory lining which it attacks in the adult. The mumps virus, on the other hand, did not induce specific abnormalities although the chicks died within five days. Influenza A virus is not teratogenic for embryos of the fourth incubation day and thereafter, which agrees in principle with the original observations of Gregg (136) that the teratogenic effects of the rubella virus on the human embryo are exerted during the early months of pregnancy.

Synthesis in the embryo.—The embryonic stages like the advanced organism face the problem of gaining energy and building living material of characteristic composition with metabolic tools of limited synthetic capacity. We know much less of the synthetic capacities of embryonic than of adult vertebrates. Schweigert *et al.* (59) injected tryptophane into eggs on the seventh incubation day and found a significant increase in the nicotinic acid content

of the entire egg. However, even earlier than this, on the fourth day, the chick can convert tryptophane (or nicotinic acid) to nicotinamide, according to Ackermann & Taylor (60). These syntheses, it must be noted, cannot be attributed to intestinal biota. In the human fetus the situation is doubtful. Although earlier work indicated that the fetal tissues contain less nicotinic acid than corresponding maternal tissues, Dean & Holman (61) find equal amounts in the blood cells of the placental cord and of the mother. Blood ascorbic acid of the human newborn is distinctly higher than that of the mother but venous blood from the cord exceeds both the fetal and maternal values [Hamil *et al.* (62)], indicating concentration though not necessarily synthesis in the placenta.

Popják (63, 64) contributes evidence which goes far to refute the idea that the fetus gains its phospholipids by placental transmission. Four hours after injecting pregnant rats, guinea pigs, and rabbits with dibasic sodium phosphate labelled with P^{32}, the phospholipids isolated from the fetal liver and placenta showed far greater activity than the phospholipids of the fetal carcass and brain and the maternal plasma. Direct injection of inorganic phosphate into the fetus *in utero* confirms his conclusion that the fetus, and especially its liver, synthesizes phospholipid at least insofar as the phosphorylating step is concerned. Fatty acids and cholesterol can pass the placental barrier of the rat in essentially intact condition according to Goldwater & Stetten (65). After injecting heavy water into pregnant rats, the latter found higher deuterium concentration in the fatty acids of the fetus than in the maternal liver, commonly regarded as the main site of fatty acid synthesis. However when deuterio-fatty acids were fed the mother, much lower concentrations of deuterium occurred in the fetal fatty acids since placental transfer is rather slow. Active fetal lipogenesis is therefore highly probable.

Novikoff & Potter (66) have correlated the synthesis of ribo- and desoxyribonucleic acids with total protein synthesis in the chick embryo. The curve for increase in total protein follows the ribonucleic acid curve, and the latter reaches its peak at just about the time when the embryo is richest in growth-promoting factors. Bodenstein & Kondritzer (67) show that nitrogen mustard (known to be a good mutagenic agent) suppresses the synthesis of desoxyribonucleic acid in amphibian larvae, with little effect on the ribo form. In spite of this, some cells continue to grow and differen-

tiate, a point of interest in relation to the problem of semiautonomous cytoplasmic systems. Schmidt *et al.* (68) find that the increase in total nucleic acid phosphorus between the unfertilized sea urchin egg and the pluteus stage is in the desoxyribo fraction; the ribonucleic acid phosphorus remains practically unchanged, so that the synthesis would seem to be from other cell constituents rather than from ribonucleic acid as previously suggested (26).

Enzyme action and development.—Several papers attempted to correlate adenylpyrophosphatase activity with relatively specific developmental events (69 to 72). Moog (69) finds apyrase activity of the chick's brain, muscle, heart, and liver is, on the whole, more closely correlated with differentiation and function than with growth. Thus in the brain phosphatase activity increases steadily from the twelfth incubation day to the first week after hatching which may be viewed as a rough correlation with brain activity. In the heart, on the other hand, apyrase activity is maximal on about the sixteenth day, with a drop at hatching and then a rise. The percentage growth rate of the heart is maximal at about the sixteenth day while its operational activity (heart rate) remains pretty steady between the tenth and nineteenth days, which would seem a notable exception to the general hypothesis associating apyrase activity with function. Moog suggests that anoxia, brought on by changes in the fetal membranes after the sixteenth day, may be involved in obscuring an otherwise general correlation. Barth & Jaeger (70) were able to distinguish three different apyrases in protein fractions from the frog's egg on the basis of pH optima and thermolability. Since these apyrases show differences in activity at several developmental periods, the possibility exists that they may be correlated with specific embryonic processes. Herrmann & Nicholas (71) fractionated the muscle protein of developing rats from the twelfth intrauterine to the thirteenth extrauterine day into three fractions, including actomyosin of Szent-Györgyi, an insoluble residue, and a soluble fraction containing most of the globulins and albumin. The insoluble fraction shows significant increase during the period of muscle differentiation. Myosin and the soluble proteins show little or no change during the same period. However on dividing the myosin into subfractions it was found that one of the subfractions shows increase during the differentiation period. In the second paper (72) the authors find that apyrase activity of developing musculature remains low during the

period of histological differentiation but increases with the onset of muscular contraction. From this time onward, apyrase activity outstrips the increase in myosin. As far as the differentiation of muscle is concerned the cytochemical studies of van Weel (127) suggest that ascorbic acid may be of importance. Glycogen was not detectable in muscle-forming cells before they had differentiated into muscle fibers.

Novikoff *et al.* (73) find that the known intermediates in the Meyerhof-Embden cycle occur in chicks of three to ten days incubation in concentrations comparable to these in mature tissues Homogenates of five to eight-day embryos can glycolyze hexose-6-phosphate, etc., and diphosphopyridine nucleotide is present. It is evident that the embryo even in these early stages has typical phosphorylating glycolysis. Nicholas (128), in a paper which reviews many aspects of early development of the rat, mentions preliminary work which indicates that carbohydrate is probably the main source of energy in the early stages.

Connon (74) has made a comparison between oxygen consumption and developmental rates of several species of amphibian embryos and their hybrids. The use of hybrids offers a unique advantage in such studies in that differences in respiratory rate possibly due to variations in yolk can be reduced. Rapid development is paralleled by heightened respiratory activity. Although hybrids in early stages show respiratory rates corresponding to those of the maternal species, when developmental rates begin to differ they are associated with corresponding respiratory changes. Collier (129) studied oxygen consumption during regeneration in *Tubifex;* no increase in oxygen uptake could be detected in early stages of regeneration, but with the onset of visible differentiation the rate of oxygen consumption rises. The distribution of Cu^{64}, injected as a chloride into the egg white, has been studied by Smith & Gray (75) using the radiograph method. During the first two days of incubation the chick localizes the copper in regions of most rapid development. The Cu^{64} pattern may reflect cytochrome oxidase distribution, since there is evidence that cytochrome oxidase may be a protein-copper complex. [See (73) for evidence of hexose-6-phosphate in chick.]

Robbie (76) shows that the sand-dollar egg is much more sensitive to cyanide than is the sea urchin egg. Nearly all its energy comes through systems requiring free oxygen. Susceptibility of the

egg to cyanide, already high to begin with, increases further with development. Anfinsen (77) finds that the respiratory inhibition produced by cyanide in *Arbacia* can be duplicated by means of naphthoquinone; a detoxifying mechanism appears to be present, judging from concentrations necessary to produce maximal inhibition in dilute and concentrated egg suspensions. In work directed primarily toward other ends, Greiff & Pinkerton (78) report on the effects of *p*-aminobenzoic acid and its analogues on oxygen consumption in the chick.

Nutrition of the early embryo.—Spratt (80, 81, 82) has described the preparation of culture media, composed of egg white or yolk extract and agar in Ringer's solution, suitable for the maintenance of the entire early chick blastoderm or portions of it for a limited time. Differentiation proceeds for at least ten to twenty-four hours after explantation to the surface of this medium, whereas degeneration is rapid in the same medium lacking egg white or yolk extract. The embryos also differentiate well in complex synthetic medium containing essential amino acids, vitamins, glucose, and salts; early differentiation will occur in the absence of all the organic constituents except glucose (82). Furthermore, in the absence of glucose alone the rest of the synthetic medium is deficient. Taylor & Schechtman (83) have confirmed the favorable effect of glucose and have found that the yolk extract medium contains a nondialyzable, nonenzymatic factor which can substitute for glucose but permits differentiation to proceed only ten to twelve hours as compared with twenty to twenty-four hours in glucose.

An interesting feature of Spratt's work is that egg white-saline-agar is a favorable medium for early morphogenesis. Egg white has a higher nutritive value than either whole egg or yolk proteins as judged by feeding experiments on young rats (84), but it contains potent enzyme and vitamin inhibitors and perhaps other substances which limit biological activity (85). Under normal conditions egg white is separated from the early blastoderm by the vitelline membrane, but under culture conditions it comes into contact with the organism. The chick would thus seem to be unaffected by the antibiotic activity of homologous egg white.

Brambell & Mills (86) found a fibrillar network in sections of the yolk sac of rabbits between the seventh and twelfth days *post coitum*. The material proved to be fibrinogen and is apparently a normal constituent of the yolk sac fluid. It must be derived from

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the maternal blood since it is present before the embryo's vascular system is formed. Moreover, it is very unlikely that the organism at this early stage can synthesize fibrinogen. The authors suggest that the fibrinogen may act as a source of nutriment and that other maternal blood proteins may also be transferred. Fawcett *et al.* (87) record interesting observations on the development of mouse and rat ova in the eye and abdominal cavity. The blastocysts induce hemorrhages and formation of new blood vessels in both localities, whereas various similarly implanted maternal tissues are without such effects. The giant cells of the trophoblast show phagocytosis and their outer protoplasm appears very vacuolated. In view of the paper by Brambell & Mills (86) one is tempted to suggest the possibility of arthrocytosis of maternal plasma and transfer of plasma proteins to the embryo. A similar transfer is postulated for the chick (93).

Embryonic blood constituents.—Although the extent to which the early embryo's plasma may be of maternal origin remains obscure (93, 94), the passive transfer of proteins after birth seems quite certain (88 to 92). Charlwood & Thomson (88) find beta- and gamma-globulin hardly discernible electrophoretically in lamb sera before the ingestion of colostrum. Gamma-globulin shows a large increase after the transfer of colostrum, but β-globulin is apparently not transferred passively. Smith (89) could hardly detect γ-globulin in the calf's blood at birth. A specific lactoglobulin present in colostrum and to lesser degree in milk readily passes through the intestinal wall into the blood of the newborn calf. Hansen & Phillips (90) also observed the lack of γ-globulin in the calf at birth and its appearance twenty-four hours after the ingestion of colostrum. Apparently the permeability of the intestine changes very rapidly, since calves given colostrum twenty-four hours after parturition do not show the increase in γ-globulin. Lemetayer *et al.* (91) find that tetanus and diphtheria antitoxins can pass the placental barrier in the horse only if the mare's antitoxin content approaches one international unit. With lower maternal titers the transfer is wholly by means of colostrum. Vogelsang & Kryvi (92) find a high correlation between positive Schick tests in women and their newborn infants.

Using precipitin tests Schechtman (93) detected common antigens (or combining groups) in early chick embryos and in adult fowl serum. The common constituent appears to be present

in yolk also and the suggestion is made that yolk pseudoglobulin is transferred from yolk to embryo. Nace & Schechtman (94) find the vitelloid constituent in the chick embryo's blood from at least the third day on. One or more nonvitelloid constituents (or combining groups), which may be blood albumin, are first detectable on the fifth or sixth day of incubation.

Partridge (96) and Bacon & Bell (97) find fructose and inositol in the blood of the fetal sheep although both are absent from adult blood. Contrary to earlier work, glucose also occurs in the fetal blood. The work of Wise *et al.* (101) suggests that high potassium content may be characteristic of fetal erythrocytes. Although sodium predominates in erythrocytes of adult cattle, the young calf shows a predominance of potassium with sodium mainly in the serum. Porter & Sanger (95) conclude that in both fetal and adult hemoglobin, valine is the only terminal amino acid. Assuming 66,000 as the molecular weight of fetal hemoglobin, it has only 2.6 terminal valyl residues as compared with 5 for the adult. Judging fetal hemoglobin by its greater resistance to denaturation by sodium hydroxide, Jonxis (133) finds the fetal form alone is present at birth in the human. It is replaced by adult hemoglobin about one hundred and twenty days after birth in the normal infant, but within about six days in the erythroblastotic infant.

The hemoglobin of embryonic rays has no greater oxygen affinity than that of the adult, according to McCutcheon (98), and thus is an exception to the general rule among vertebrates.

Serological studies.—Besides the above-mentioned papers involving serological methods (93, 94), two others have appeared (99, 100). Cooper (99) has continued work on the identity of antigens in earliest developmental stages of the frog and in the adult. Certain antigens or combining groups, probably of protein nature, are present in common. Perhaps of greater potential significance are indications that the early stages may contain antigens different from those in later stages. Weiss (100) deposited antisera (against autolysates of several adult chicken tissues) near early chick embryos and discerned a tendency toward weight increases in homologous structures. Thus, chicks subjected to antisera against adult liver autolysate, developed livers about 10 per cent heavier than those of controls although antikidney sera had no such effect on the liver. Implanted pieces of embryonic chick liver likewise caused an increase in liver weight in proportion to the total weight

of the host. From the data Weiss develops a concept of duplication of specific molecules by molecular master patterns.

Sex differentiation.—In accord with previous work by Fugo and others, Raynaud & Frilley (102) find the male and female ducts of embryonic mice are little influenced by destruction of the hypophysis. Embryos irradiated at twelve to thirteen days of development and studied at term showed only such minor deviations as fewer gonocytes and narrower seminiferous tubules. The hypophysis, and in fact the entire head, apparently exerts no control over body growth in the rabbit embryo between the nineteenth and twenty-eighth day of development [Jost (103)].

Reynaud (104) studied the effects of testosterone, injected into the pregnant mouse, on the earliest development of the mammary buds in the embryos. The male hormone induces the male type of development and, in addition, the Müllerian ducts of the female are inhibited as to size. Wolff & Wolff (105) find straightforward homologous effects of male and female hormones on the development of the penis in duck embryos. Boss & Witschi (106) injected stilbestrol into Herring gull eggs on the third, sixth, or ninth day of incubation and obtained premature and permanent puberal changes in the oviducts of both sexes. The ovary was little affected but the left testis formed ovarian cortex. Stool (107) repeated Willier's earlier work on the feminizing effects of both testosterone and estradiol on the male chick. When given together the feminizing effect of estradiol is obliterated, with intersexuality in the gonads and Müllerian ducts and marked distention of the Wolffian ducts. The latter condition is apparently caused by increased secretion and seems to be connected with the regression of the Müllerian duct.

The results of hormone injections indicate relative sensitivities but do not inform us as to factors actually operative in the embryo. We have information more pertinent to the latter in Jost's work (108) on gonadectomy in male rabbit embryos just before and after the appearance of the first somatic sex differences. The castrated male embryo shows a definite feminization, even to the absence of the prostate if the operation is performed before the prostatic bud has appeared. The testis seems to act by secretion since the Wolffian ducts are maintained after unilateral, though not after bilateral, castration. A comprehensive review of differentiation of the sex apparatus is presented by Price (131).

Experimental morphogenesis.—The prevalent concept of the derivation of muscles and skeletal elements of the lateral and ventral body wall from the somites is brought into doubt by the experiments of Rawles & Straus (110). By marking somites or lateral plate with carbon it was shown that the ventral portions of the ribs and the ventrolateral trunk musculature arise *in situ*, apparently from the lateral plate.

Holtfreter (111), continuing investigations of self neuralization discovered a few years ago by Barth, finds that media which produce cytolytic and disaggregative changes in presumptive ectoderm are neuralizing. If the tissue is maintained in good condition it does not undergo neuralization. Van Cleave (112) could not obtain neural inductions in *Amblystoma* with water soluble carcinogen (dibenzanthracene), which, in view of Holtfreter's work, raises the question whether the neuralizing effects formerly noted by Waddington & Needham (135) may not have been due indirectly to an unfavorable condition set up in the medium rather than by direct effect of the carcinogen.

Damas (113) and Gallera (114) find that the very early neural plate proper (as distinct from the neural fold region) has some of the developmental capacities of neural crest. Potentialities for typical neural differentiation arise during neurulation. The mesoderm under the posterior nonneural portion of the neural plate induces predominantly mesodermal structures in contrast with more anterior regions of the mesoderm according to Spofford (115). Harrison (116) has analyzed some factors involved in the reconstitution of the early central nervous system after removal of portions of the neural plate. The regulation involves hyperplasia and shift of tissue to the site of the wound, a shift occurring predominantly from the corresponding intact level of the plate.

Work on the developmental significance of the neural crest has continued actively (117 to 123). The neural crest of the mouse embryo, like that of amphibians and birds, contains presumptive melanophore material, according to Rawles (117), who observed the development of white hair from genetically black mouse tissue after removal of neural crest. Niu (118) finds that melanophores in the amphibian embryo are derived predominantly from the trunk neural fold and very few from the anterior and extreme posterior portions. In fact the head neural fold seems to exert an inhibiting effect on pigment-cell production by the remainder of

the fold. De Beer (119) has traced neural crest cells, using pigment inclusions and absence of yolk granules as criteria for ectodermal cells, to the visceral cartilages, odontoblasts, and possibly osteoblasts. A discussion of the limitations and values of the germ layer theory is included. Levi-Montalcini & Amprino (120) find that the ciliary ganglia of the chick develop after removal of various portions of the neural tube. The ganglia develop *in situ* from the mesenchyme, but the authors think the ultimate derivation is from the head neural crest. Detwiler (121) excised the neural crest in *Amblystoma* and found that the limbs functioned normally and motor fibers could enter the limb despite the presumed absence of sheath cells (neural crest derivatives). The limbs functioned quite normally. Van Campenhout (122) discusses the origin of the intrinsic neurons of the gut wall. A review of recent work on the origin of the autonomic nervous system is presented by Yntema & Hammond (123).

Barron (124) has made an analysis of factors involved in the reduction of the number of motor neurons after removal of the wing bud in the chick. The reduction is first clearly manifested when the first bipolar neuroblasts appear in the mantle layer. The presence of the peripheral field thus seems causally related to the differentiation of bipolar neuroblasts from the unipolar condition, after which the bipolar cells become active as inductors, inducing indifferent cells of the mantle to become neuroblasts. Hamburger (125) describes mitotic activity in the spinal cord of the chick and points out that the growth of the tube after the eighth day is largely the result of differentiation processes rather than proliferation.

Amprino (126) suggests that the structure of bone tissue is related to the varying growth rates of different stages. During periods of rapid growth the resorption lacunae are large and the pieces of secondary bone are coarse and irregular; when growth slows down and resorption processes are presumably less intense, the texture of the bone becomes finer.

LITERATURE CITED

1. Öhman, L. O., *Arkiv Zool.* [A]**39**, 1–7 (1947)
2. Wicklund, E., *Nature*, **161**, 556 (1948)
3. Monroy, A., and Montalenti, G., *Biol. Bull.*, **92**, 151–61 (1947)
4. Monroy, A., *J. Cellular Comp. Physiol.*, **30**, 105–9 (1947)

5. Brooks, M. M., *Science*, **106**, 320 (1947)
6. Connors, W. M., and Scheer, B. T., *J. Cellular Comp. Physiol.*, **30**, 271–83 (1947)
7. Swyer, G. I. M., *Biochem. J.*, **41**, 413–17 (1947)
8. Swyer, G. I. M., *Biochem. J.*, **41**, 409–13 (1947)
9. Hechter, O., and Hadidian, Z., *Endocrinology*, **41**, 204–5 (1947)
10. Sherber, D. A., Birnberg, C. H., and Kurzrok, R., *Endocrinology*, **42**, 20–25 (1948)
11. Perlman, P. L., Leonard, S. L., and Kurzrok, R., *Endocrinology*, **42**, 26–30 (1948)
12. Swyer, G. I. M., *Nature*, **160**, 433 (1947)
13. Leonard, S. L., Perlman, P. L., and Kurzrok, R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 517–18 (1947)
14. Cheney, R. H., *Biol. Bull.*, **94**, 16–24 (1948)
15. Rybak, B., *Compt. rend.*, **225**, 701–2 (1947)
16. Simpson, S. A., and Williams, P. C., *Nature*, **161**, 237 (1948)
17. Chang, M. C., *J. Gen. Physiol.*, **31**, 385–410 (1948)
18. Huskins, C. L., *American Naturalist*, **81**, 401–34 (1947)
19. Huskins, C. L., *Nature*, **161**, 80–83 (1948)
20. Prokofyeva-Belgovskaya, A. A., *J. Genetics*, **48**, 80–98 (1947)
21. Schultz, J., *Cancer Research*, **7**, 41–42 (1947)
22. Spiegelman, S., *Cancer Research*, **7**, 42–43 (1947)
23. Monod, J., *Growth*, **11**, 223–90 (1947)
24. Sonneborn, T. M., *Growth*, **11**, 291–308 (1947)
25. van Wagtendonk, W. J., *J. Biol. Chem.*, **173**, 691–704 (1948)
26. Brachet, J., *Growth*, **11**, 309–24 (1947)
27. Strong, L. C., *Proc. Soc. Exptl. Biol. Med.*, **67**, 46–49 (1948)
28. Callan, H. G., *Nature*, **161**, 440 (1948)
29. Villee, C. A., *J. Gen. Physiol.*, **31**, 337–45 (1948)
30. Briggs, R., *J. Exptl. Zoöl.*, **106**, 237–66 (1947)
31. Moore, J. A., *J. Exptl. Zoöl.*, **105**, 329–48 (1947)
32. Moore, J. A., *J. Exptl. Zoöl.*, **108**, 127–54 (1948)
33. Warkany, J., and Roth, C. B., *J. Nutrition*, **35**, 1–12 (1948)
34. Hainsborough, L. A., *Growth*, **11**, 77–88 (1947)
35. Strong, L. C , and Hollander, W. F., *J. Nat. Cancer Inst.*, **8**, 79–82 (1947)
36. Gillis, M. O., Heuser, G. F., and Norris, L. C., *J. Nutrition*, **35**, 351–64 (1948)
37. Hainsborough, L. A., *Growth*, **11**, 177–84 (1947)
38. Couch, J. R., Cravens, W. W., Elvehjem, C. A., and Halpin, J. G., *J. Nutrition*, **35**, 57–72 (1948)
39. Couch, J. R., Cravens, W. W., Elvehjem, C. A., and Halpin, J. G., *Anat. Record*, **100**, 29–48 (1948)
40. Landauer, W., *J. Exptl. Zoöl.*, **105**, 145–72 (1947)
41. Landauer, W., *J. Exptl. Zoöl.*, **105**, 317–28 (1947)
42. Moseley, H. R., *J. Exptl. Zoöl.*, **105**, 279–316 (1947)
43. Zwilling, E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 192 (1948)
44. Landauer, W., *Endocrinology*, **41**, 489–93 (1947)

45. DAVIS, M. E., FUGO, N. W., AND LAWRENCE, K. G., *Proc. Soc. Exptl. Biol. Med.*, **66**, 638–39 (1947)
46. BRANSON, H., BANKS, H. W., JR., AND DODSON, L. B., *Science*, **106**, 637–38 (1947)
47. ADAMS, A. E., AND BULL, A. L., *Anat. Record*, **100**, 729 (1948)
48. LYNN, W. G., *Biol. Bull.*, **94**, 1–15 (1948)
49. MANDEL, P., STOLL, R., AND BIETH, R., *Compt. rend. soc. biol.*, **141**, 676–78 (1947)
50. MEYER, R. K., KOSMO, L. S., AND MCSHAN, W. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 111–13 (1947)
51. ROSTAND, J., *Compt. rend. soc. biol.*, **141**, 563–64 (1947)
52. ROSTAND, J., *Compt. rend. soc. biol.*, **141**, 565 (1947)
53. HSU, C. Y., *Anat. Record*, **100**, 79–90 (1948)
54. DETWILER, S. R., COPENHAVER, W. M., AND ROBINSON, C. O., *J. Exptl. Zoöl.*, **106**, 109–23 (1947)
55. RANZI, S., *Nature*, **160**, 712 (1947)
56. WOLFF, E., AND LUTZ, H., *Compt. rend. soc. biol.*, **141**, 901–3 (1947)
57. WOLFF, E., AND KAHN, J., *Compt. rend. soc. biol.*, **141**, 915–16 (1947)
58. HAMBURGER, V., AND HABEL, K., *Proc. Soc. Exptl. Biol. Med.*, **66**, 608–17 (1947)
59. SCHWEIGERT, B. S., GERMAN, H. L., AND GARBER, M. J., *J. Biol. Chem.*, **174**, 383–84 (1948)
60. ACKERMANN, W. W., AND TAYLOR, A., *Proc. Soc. Exptl. Biol. Med.*, **67**, 449–52 (1948)
61. DEAN, R. F. A., AND HOLMAN, W. I. M., *Nature*, **161**, 439 (1948)
62. HAMIL, B. M., MUNKS, B., MEYER, E. Z., KAUCKER, M., AND WILLIAMS, H. H., *Am. J. Diseases Children*, **74**, 417–33 (1947)
63. POPJÁK, G., *Nature*, **160**, 841–42 (1947)
64. POPJÁK, G., *Biochem. J.*, **42**, xl (1948)
65. GOLDWATER, W. H., AND STETTEN, D., JR., *J. Biol. Chem.*, **169**, 723–38 (1947)
66. NOVIKOFF, A. B., AND POTTER, V. R., *J. Biol. Chem.*, **173**, 233–38 (1948)
67. BODENSTEIN, D., AND KONDRITZER, A. A., *J. Exptl. Zoöl.*, **107**, 109–22, (1948)
68. SCHMIDT, G., HECHT, L., AND THANNHAUSER, S. J., *J. Gen. Physiol.*, **31**, 203–7 (1948)
69. MOOG, F., *J. Exptl. Zoöl.*, **105**, 209–20 (1947)
70. BARTH, L. G., AND JAEGER, L., *J. Cellular Comp. Physiol.*, **30**, 111–30 (1947)
71. HERRMANN, H., AND NICHOLAS, J. S., *J. Exptl. Zoöl.*, **107**, 165–76 (1948)
72. HERRMANN, H., AND NICHOLAS, J. S., *J. Exptl. Zoöl.*, **107**, 177–81 (1948)
73. NOVIKOFF, A. B., POTTER, V. R., AND LEPAGE, G. A., *J. Biol. Chem.*, **173**, 239–52 (1948)
74. CONNON, F. E., *J. Exptl. Zoöl.*, **105**, 1–24 (1947)
75. SMITH, E. E., AND GRAY, P., *J. Exptl. Zoöl.*, **107**, 183–216 (1948)
76. ROBBIE, W. A., *J. Gen. Physiol.*, **31**, 217–32 (1948)
77. ANFINSEN, C. B., *J. Cellular Comp. Physiol.*, **29**, 323–32 (1947)
78. GREIFF, D., AND PINKERTON, H., *J. Exptl. Med.*, **87**, 175–98 (1948)
79. WILLIAMSON, M. D., *J. Biol. Chem.*, **174**, 631–36 (1948)
80. SPRATT, N. T., JR., *Science*, **106**, 452 (1947)

81. SPRATT, N. T., JR., *J. Exptl. Zoöl.*, **106**, 345–65 (1947)
82. SPRATT, N. T., JR., *J. Exptl. Zoöl.*, **107**, 39–64 (1948)
83. TAYLOR, K. W., AND SCHECHTMAN, A. M., *J. Exptl. Zoöl.* (In press)
84. HESS, W. C., KRAMKE, E. H., FRITZ, J. C., AND HOWARD, H. W., *Proc. Soc. Exptl. Biol. Med.*, **67**, 552–56 (1948)
85. LINEWEAVER, H., AND MURRAY, C. W., *J. Biol. Chem.*, **171**, 565–81 (1947)
86. BRAMBELL, F. W. R., AND MILLS, I. H., *J. Exptl. Biol.*, **23**, 332–45 (1947)
87. FAWCETT, D. W., WISLOCKI, G. B., AND WALDO, C. M., *Am. J. Anat.*, **81**, 413–44 (1947)
88. CHARLWOOD, P. A., AND THOMSON, A., *Nature*, **161**, 59 (1948)
89. SMITH, E. L., *J. Dairy Sci.*, **31**, 127–38 (1948)
90. HANSEN, R. G., AND PHILLIPS, P. H., *J. Biol. Chem.*, **171**, 223–27 (1947)
91. LEMETAYER, E., NICOL, L., JACOB, L., GIRARD, O., AND CORVAZIER, R., *Ann. inst. Pasteur*, **73**, 297–322 (1947)
92. VOGELSANG, T. M., AND KRYVI, *J. Hyg.*, **44**, 437–41 (1946)
93. SCHECHTMAN, A. M., *J. Exptl. Zoöl.*, **105**, 329–48 (1947)
94. NACE, G. W., AND SCHECHTMAN, A. M., *J. Exptl. Zoöl.*, **108**, 217–34 (1948)
95. PORTER, R. R., AND SANGER, F., *Biochem. J.*, **42**, 287–94 (1948)
96. PARTRIDGE, S. M., *Biochem. J.*, **42**, 238–48 (1948)
97. BACON, J. S. D., AND BELL, D. J., *Biochem. J.*, **42**, 397–405 (1948)
98. MCCUTCHEON, F. H., *J. Cellular Comp. Physiol.*, **29**, 333–44 (1947)
99. COOPER, R. S., *J. Exptl. Zoöl.*, **107**, 397–438 (1948)
100. WEISS, P., *Yale J. Biol. Med.*, **19**, 236–78 (1947)
101. WISE, G. H., CALDWELL, M. J., PARRISH, D. B., FHIPSE, R. J., AND HUGHES, J. S., *J. Dairy Sci.*, **30**, 983–93 (1947)
102. RAYNAUD, A., AND FRILLEY, M., *Compt. rend.*, **225**, 596–98 (1947)
103. JOST, M. A., *Compt. rend.*, **225**, 322–24 (1947)
104. RAYNAUD, A., *Annales endocrinologie*, **8**, 248–53 (1948)
105. WOLFF, E., AND WOLFF, E., *Compt. rend. soc. biol.*, **141**, 916–17 (1947)
106. BOSS, W. R., AND WITSCHI, E., *J. Exptl. Zoöl.*, **105**, 61–78 (1947)
107. STOOL, R., *Compt. rend.*, **225**, 598–600 (1947)
108. JOST, A., *Proc. Soc. Exptl. Biol. Med.*, **66**, 302–3 (1947)
109. OPPENHEIMER, J. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 49–50 (1947)
110. RAWLES, M. E., AND STRAUS, W. L., *Anat. Record*, **100**, 755 (1948)
111. HOLTFRETER, J., *J. Exptl. Zoöl.*, **106**, 197–222 (1947)
112. VAN CLEAVE, C. D., *J. Elisha Mitchell Sci. Soc.*, **63**, 133–40 (1947)
113. DAMAS, H., *Arch. biol.* (*Liége*), **58**, 15–55 (1947)
114. GALLERA, J., *Arch. biol.* (*Liége*), **58**, 221–64 (1947)
115. SPOFFORD, W. R., *J. Exptl. Zoöl.*, **107**, 123–59 (1948)
116. HARRISON, R. G., *J. Exptl. Zoöl.*, **106**, 27–84 (1947)
117. RAWLES, M. E., *Physiol. Zoöl.*, **20**, 248–66 (1947)
118. NIU, M. C., *J. Exptl. Zoöl.*, **105**, 79–112, (1947)
119. DE BEER, G. R., *Proc. Roy. Soc. London*, [B]**134**, 377–98 (1947)
120. LEVI-MONTALCINI, A., AND AMPRINO, R., *Arch. biol.* (*Liége*), **58**, 265–88 (1947)
121. DETWILER, S. R., *J. Exptl. Zoöl.*, **106**, 299–312 (1947)
122. VAN CAMPENHOUT, E., *Arch. biol.* (*Liége*), **58**, 1–14 (1947)
123. YNTEMA, C. L., AND HAMMOND, W. S., *Biol. Revs. Cambridge Phil. Soc.*, **22**, 344–59 (1947)

124. BARRON, D. H., *J. Comp. Neurol.*, **88**, 93–127 (1948)
125. HAMBURGER, V., *J. Comp. Neurol.*, **88**, 221–84 (1948)
126. AMPRINO, R., *Arch. biol. (Liége)*, **58**, 315–30 (1947)
127. VAN WEEL, P. B., *J. Anat.*, **82**, 49–57 (1948)
128. NICHOLAS, J. S., *Quarterly Rev. Biol.*, **22**, 179–95 (1947)
129. COLLIER, J. G., *Biol. Bull.*, **92**, 167–77 (1947)
130. GABRIO, B. W., AND SALOMON, K., *Endocrinology*, **42**, 73–76 (1947)
131. PRICE, D., *Physiol. Zoöl.*, **20**, 213–47 (1947)
132. BARRON, E. S. G., SEEGMILLER, J. E., MENDES, E. G., AND NARAHARA, H. T., *Biol. Bull.*, **94**, 267–74 (1948)
133. JONXIS, J. H. P., *Nature*, **161**, 850 (1948)
134. MIRSKY, A. E., *Science*, **84**, 333 (1936)
135. WADDINGTON, C. H., AND NEEDHAM, D. M., *Proc. Roy. Soc. (London)* [B]**117**, 310–17 (1935)
136. GREGG, N. M., *Trans. Ophthalmol. Soc. Australia*, **3**, 35–47 (1942)

REPRODUCTION[1]

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The Ovary and Ovulation

Human ova.—An eighty-year quest for early human embryos, dating from the discovery of the Reichart ovum of 1868, reached a climax in the work of Rock, Hertig & Menkin (132, 171). The youngest embryos, two of two cells each and two of three cells, were obtained by exposure of ova from unruptured follicles to human sperm in watch glasses. The naturally fertilized ovum is believed to reach the uterus on the third day, and on the sixth day it is a blastocyst of three tissues and begins the erosion of the maternal endometrium. On the ninth day, the trophoblast has been seen entering a maternal sinusoid. Development has been followed in this series till the fourteenth day, when the primitive streak appears. Robertson *et al.* (170) well illustrated and described a normal human embryo of seventeen days.

Histochemistry of the ovary.—In a critical examination of histochemical reactions of the ketosteroids, Claesson & Hillarp (34) concluded, in agreement with Gomori (75), that the substance reacting with phenylhydrazine was, in all probability, plasmal, and that at the present time it is not possible to demonstrate histochemically any carbonyl group of a ketosteroid. These authors have shown a substance in the ovary, having the polarization characteristics of cholesterol, which they believe to be the precursor of estrogenic hormone. In preovulatory follicles, the precursor is stored in the theca interna in the rat and rabbit, and in the interstitial gland of rat, rabbit, and guinea pig; it is lowest in amount in estrus and diestrus (32, 33). Analyses of total cholesterol in the ovaries of cyclic, pregnant, and lactating rats led Perlman & Leonard (149) to conclude that a close relationship existed between cholesterol and progesterone. In a study of glycogen and carbohydrate-protein complexes in the ovary of the rat during the estrus cycle, Harter (94) found the normally developing ovum to be the only cell with appreciable amounts of glycogen, while ovum, zona

[1] This review covers the period from April 1, 1947 to June 1, 1948.

pellucida, granulosa cells of the follicle, luteal cells, macrophages, follicular fluid, intercellular substance, and basement membranes contained stainable glycoprotein. Increased cytoplasmic glycoprotein of the granulosa cells was related to antrum formation and follicular growth. The glycoproteins of normal and atretic ova differed in their solubility properties. The zona pellucida reacted to extractives in such a way as to suggest that its penetration by sperm cells could be due to a local increase in hydrogen ion concentration. An elegant method was used by Claesson (35) to show rather conclusively the absence of smooth muscle in the wall of the graffian follicle of cow, swine, rabbit, and guinea pig, when the application of classical staining methods failed to distinguish between smooth muscle and connective tissue. This demonstration depends on a decisive difference between the intrinsic molecular birefringence of muscle and the form birefringence of connective tissue. In studies of rabbit ovaries from sex differentiation to maturity, Duke (50) concluded that the connective tissue of the ovary is in a dynamic state and that the maturation of a follicle involves the thinning out and disappearance of the overlying tunica albuginea.

The outlines of a concept of follicular growth and ovulation may be drawn from some of the work reviewed above. It is suggested that the activity of enzymes acting on connective tissue is involved. Such enzymes (mucinases, spreading factors) have become known in recent years, and their action is, briefly, to depolymerize mucopolysaccharides of the type present in the ground substance of connective tissue. Presumably this action is reversible. The follicle would then be accommodated by growth into a region of depolymerized (less viscous, less resistant) connective tissue stroma. At ovulation, a dissolution of the connective tissue of the follicular wall and the tunica albuginea would occur by a similar process. The nature and direction of these actions are predicated on the secretion of hormones which control the several stages and which have local effects on the cells of the ovarian stroma.

Pluripotentialities of the ovary.—Hill (99) showed that mouse ovaries grafted into the ears of the donors themselves, or into the ears or testes of male recipients, permitted their adrenalectomized hosts to survive for a longer (if variable) time; cutting the mesovarium and with it the ovarian artery, vein, and nerves similarly induced an ovarian secretion of hormones with corticoid activity

(100). Moore & Wang (136) produced chemical destruction of the ovarian cortex prepuberally in rats, guinea pigs, cats, and opossums; study up to a year later revealed active follicular development, with little tendency for medullary cords to develop in a testicular direction.

Ovarian transplants.—Butcher (28) showed that transplanted ovaries of rats developed better if the capsule was retained, and that even *in situ* decapsulation of the ovary retarded its growth. Harris & Eakin (92) found that grafts of rat ovaries into paired normal and ovariectomized rats were larger and better vascularized in the latter. Estrus occurred generally in autogenous, sister to sister, and intrastrain grafts, less often in interstrain grafts, and was absent in heterologous grafts.

Corpus luteum and fertilization.—As is well known from the work of Cole *et al.* (39) the pregnant mare shows the remarkable phenomenon of ovulation and corpus luteum formation in the second month of pregnancy. Whether these animals come into heat at this time seems not to be definitely known [Cole (37)], nor has a case of superfetation been seen or reported, to the knowledge of the reviewer. Preliminary attempts by Amoroso *et al.* (5) to effect fertilization of ova recovered from pregnant mares were stated to have failed. In studies of the Wisconsin group (18) rabbits were artificially ovulated with gonadotrophin given intravenously and artificially inseminated; liberated ova were recovered and examined forty-five hours later. Prior administration of progesterone for ten days suppressed the fertilizability of these ova, an effect partially nullified by estrogen. In a comparable experiment, the fertilizability of eggs from superovulated rabbits was around 80 per cent in juvenile, estrus, and anestrus does, but was zero at five days post partum (137). From the work of Harter (94) already quoted, it may be suggested that a likely locus of the barrier to fertilization is the zona pellucida whose specific glycoprotein may change under the influence of the luteal hormone.

Corpus luteum, progesterone, progestational proliferation.—In the corpus luteum of the pregnant rat, Bassett (11), on the basis of mitosis counts, distinguished an early proliferative phase and a late phase of cell hypertrophy. Forbes (66) showed that plasma levels of progesterone in the pregnant mouse were high till the seventh day and low in late pregnancy. These two studies would appear to relate progesterone secretion to the proliferative phase

of the corpus luteum. Peckham & Greene (146) reported production of deciduomata in the unilaterally pregnant rat till the seventh day of pregnancy, but not on the ninth day, and this failure was not corrected by removal of the pregnant cornu on the seventh day. Other experiments on the physiology of deciduomata were: failure of established deciduomata to inhibit the development of a new crop in the rat (147); inefficacy of α-tocopherol and prolactin, and a slight action of desoxycorticosterone in their production (165); failure of deciduomata to prolong pseudopregnancy in the mouse (112).

Female Reproductive Tract

The menstrual cycle, human and primate.—Coiled arterioles similar to those in rhesus were described by Kaiser (109) in the uterine mucosae of the baboon, chimpanzee, and gibbon. The significance of coiling for menstruation seems to have been reduced by this author's studies in platyrrhine monkeys, where no coiled arterioles were found (110). Since menstruation is microscopic in the latter forms and gross in those primates whose endometria contained coiled arterioles, it was considered possible that these vessels may regulate the amount of bleeding once the menstrual process has been established. From the work of Bensley (14), mitotic counts in the endometrium of the macaque showed peaks in the presence of a large follicle, as well as just before and after ovulation, and low values in the late luteal phase. Studies of Atkinson & Engle (9) and Arzac & Blanchet (6) essentially agreed that the alkaline phosphatase of the uterine epithelium of man paralleled the mitotic rate in being high during the proliferative phase, reduced in the secretory phase, and absent several days premenstrually and during menstruation. Glycogen showed an inverse relationship with the enzyme (6). In ovariectomized monkeys, the enzyme was present in glands and surface epithelium after estrogen treatment and was reduced following the addition of progesterone (9).

Abarbanel (1) produced cyclical changes in human cervical mucus by the use of estradiol and stilbestrol in castrates. Progesterone, testosterone propionate, and methyltestosterone failed to stimulate the flow of cervical mucin. Atkinson *et al.* (10) demonstrated relatively constant amounts of mucus throughout the cycle in the apical cytoplasm of cervical glandular epithelial cells,

although active secretion was rhythmic. It would thus seem to be a promising approach to study the physicochemical properties of mucus in cervical cells, since a change in state (e.g., depolymerization) under the influence of estrogens may be one condition, at least, of its release.

The question of threshold bleeding was reopened by Clark (36). In a female chimpanzee castrated for several years and receiving constant doses of estrogen and progesterone the sex skin waxed and waned and menstruation occurred periodically. These two indicators were dissociated in time, however, creating a situation difficult to reconcile with the theory of fluctuation in steroid output of the adrenal as originally suggested by Long & Zuckerman. The author's proposal of a threshold alteration in the responding organs redefines the problem. Continuing their studies on the baboon, Gilbert & Gillman (72) found that administration of testosterone propionate to castrated males or females gave a turgescence response within the first week similar to that following estradiol; then new properties emerged and there occurred an active deturgescence at which point estrogens were relatively ineffective in restoring turgescence. Males were more refractory than females in this respect (73). Methods employed several years ago by Ogston *et al.* (143) might contribute to the elucidation of hormonal effects on turgescence in primates. It was then shown that estrogens evoked a connective tissue reaction and that mucoproteins appeared in the exudates of swollen tissues. The effect of androgens on these reactions should prove instructive.

Some earlier experiments of Engle were recalled by a study of Ferin (60) in which ovariectomized women with implants of crystalline stilbestrol were given 40 mg. testosterone per day for six or seven days. There occurred in several cases a withdrawal hemorrhage, with a latency of eighteen to one hundred and fifteen hours. Since no progesterone changes were seen in the mucosa this treatment was claimed to be clinically advantageous as a way of avoiding cystic endometrial hyperplasia in the bearers of estrogen implants. Comparable findings by Marvin (127) in the rodent may conveniently be cited here.

Histochemistry of the uterus (see also previous section).—An intensive study by Pritchard (158) of alkaline phosphatase in the uterus of the pregnant rat showed general agreement with earlier reports, although the interpretation was modified. In the phase

of proliferation and differentiation the enzyme was detected within the nucleus; during specific functional activity it was exclusively cytoplasmic. In contradiction with the Harvard group, least activity was found in regions of the decidua, trophoblast, and metrial gland which are engaged in glycogen storage [cf. also Arzac (6)].

Physiology of the reproductive tract.—It was shown by Kaiser (111) that the well-known actions of estrogens on endometrial vascular responses in intraocular endometrial homotransplants of rabbit uterus were unaffected by the powerful acetylcholine inhibitor, atropine. The author concluded that the estrogen effect was not cholinergic and that such changes in total acetylcholine as had been observed previously were of myometrial origin. Strong peristaltic waves were observed by Odor & Blandau (142) in the tubal sac of the rat oviduct, indicating an additional mechanism for transport of ova. Hamilton (85) found the cervix uteri of the rat to show a gradient from vagina to uterus in structure and in response to estrogens.

Miscellaneous.—Factors influencing the growth and development of the mammalian reproductive tract were reviewed by Price (157). Castration of mice at birth permitted normal development, till at least three and a half months of age, of the external genitalia and of the os clitoris (161). In hamsters, male accessories regressed following castration at birth, but female accessories progressed normally until twenty-five days of age (117). Studies off the beaten path referred to phases of the sex cycle in the mole (74), tree kangaroo (128), and hedgehog (179). Harrison (93) contributed a considerable study of the ovary of the goat.

Pregnancy and Parturition

Van Wagenen (197) observed in the pregnant macaque three instances of spontaneous death of the fetus (diagnosed by x-ray) with viable placenta, paralleling earlier work in which the fetus was removed without disturbing the placenta. All animals continued in the physiological state of pregnancy, and the pyeloureteral dilatation which arose or persisted was shown to be independent of the presence of the fetus, but contingent on the functioning placenta. Zondek *et al.* (206) premised that with the death of the fetus, the first organ to die would be the placenta, and that this would be reflected in failure to give a pregnancy test. This thesis

should be appraised in the light of Zondek's own finding of a case of fetal death with viable placenta and persistence of urinary estrogens and gonadotrophins (203), as well as of the numerous demonstrations in primates and other mammals of placental retention and function following removal or destruction of the fetus. Studies such as these, nevertheless, will be expected to reveal the incidence of intrauterine death, with or without placental survival, at various stages of pregnancy in man. Of the correlates of pregnancy, the excretion of pregnanediol received considerable attention from the standpoints of assay techniques and clinical interpretation (13, 17, 43, 82, 104, 123, 153, 159, 183). Davis & Fugo (42) found that administration of large doses of testosterone propionate or stilbestrol to normal pregnant women did not modify the excretion of pregnanediol, contradicting reports of others on the efficacy of stilbestrol in this respect (164).

Pregnancy as a variable complicating hypertension was studied by Grollman (79) in the rat, rabbit, and dog. The primary consideration was shown to be the relative increase in the vascular bed due to the presence of the placenta. The fall in blood pressure was thus greater in small than in large animals, and greater with large than with small litters. Pseudopregnancy and the presence of deciduomata were ineffective. Smith & Smith (182) reviewed the toxemias of pregnancy. Measurements of uterine pressures at various stages of labor by Torpin (195) showed high maximal pressures (up to 100 mm. mercury) and maintenance of positive pressures between contractions.

Risman (167) described a remarkable sequence of events occuring at parturition in the opossum, the outstanding feature of which was the breaking of connective tissue barriers by the fetuses. This process calls to mind the dissolution of structures in the pubic symphyses of some rodents.

Placenta and placental barrier.—Two notes dealt with the source of fetal iron in the guinea pig and rat, using radioiron as a tracer. In the guinea pig it was computed by Flexner *et al.* (62) that iron available from maternal plasma at the fortieth and fiftieth day, and near term, comfortably exceeded the fetal demand. Maternal red cells were regarded as an unlikely source since at the fortieth day they yielded at most one third of the fetal iron requirement. In rats rendered anemic by periodic bleeding evidence was derived by Everett & Henderson (58) that red cells

crossed the placental barrier. In further studies of the Carnegie group, permeability of the human placenta to sodium was shown to increase seventy times between the ninth and thirty-sixth week, then to decrease rapidly till term, with a high safety factor at all times. Sodium passage in the middle of the ninth decile of pregnancy for sow, goat, cat, guinea pig, rabbit, rat, and man corresponds closely with the type of placentation according to Grosser's scheme (63). From studies of cholesterol distribution in maternal, umbilical, and fetal blood, Sadowsky *et al.* (172) found little evidence of special fetal involvement in cholesterol metabolism. The partition of injected phosphorus-labelled disodium phosphate between the phospholipids of maternal and fetal tissues in experiments of Popják (155) with rats, guinea pigs, and rabbits indicated fetal liver and placenta to be sites of synthesis. Since very little radiophosphorus injected into fetuses appeared in the mother, it was considered highly probable that the fetus synthesizes all its phospholipids. Human trophoblast was cultivated by Gurchot *et al.* (81) in the anterior chamber of the rabbit eye and was stated to secrete chorionic gonadotrophin and steroid hormones. Evidence was given by Stewart *et al.* (186) supplementing the earlier findings of Gey, that human placenta grown in tissue culture secreted gonadotrophin, in amounts according with the degree of proliferation of Langhans cells in the explants; estrogen was not detected.

Relaxin.—Work on relaxin represented largely extensions of activities reported last year (164). Hall & Newton (84) consider relaxin an undisputed hormonal entity whose action is essentially that of a potentiator of the action of estrogens on the symphysis. In the pubic symphysis of the young female guinea pig Talmage (193) described the gradual replacement of cartilage by connective tissue, a process that was completed in the first pregnancy. Castration reversed this sequence in the direction of chondrification. Estrogen caused cartilage replacement while relaxin caused a dissolution of the connective tissue formed in this site. Events in the pubic symphysis of the mouse described by Hall (83) also involved a reversible transformation of cartilage and connective tissue. The effect of relaxin on cartilage and connective tissue was stated to occur *in vitro* (192). An analysis of events so far described in the pubic symphysis would seem to point to a role of an enzyme of the mucinase class. The rapid softening of the connective tissue

of the symphysis by relaxin suggests a process of depolymerization of connective tissue elements, with attendant loss of rigidity. Whether relaxin induces secretion of the enzyme, or itself posesses this property, is speculative at this stage, as also is the nature of estrogen action in the preparatory process.

The Mammary Glands and Lactation

The topic "Lactation, Function and Product" was reviewed by some score of British authorities (22), bringing a knowledge of all phases of this subject practically to date. Developmental and structural features of the mammary gland were also covered. Technical aspects of this review refer to British practice. A review by Petersen (151) emphasized lactation in bovines.

Mammary glands.—It has become accepted that the anterior pituitary gland secretes factors which affect mammary ducts and alveoli directly, without the mediation of steroid hormones from either the gonads or adrenals (65). The latter hormones find their principal expression in stages preparatory to, and during, secretion. It may be pointed out that proliferation of the mammary gland may involve not merely the "growth" of ducts and lobules which insinuate themselves by brute force into the surrounding connective tissue, but also preparation of the connective tissue stroma as well as of the mammary tree. Analysis of this interaction may assist in defining the prerequisites for growth of the mammary gland in different species. It is perhaps possible to see as one aspect of this the increased hydration of the mammary gland of the rat shown by Folley & Greenbaum (65) to occur under the influence of desoxycorticosterone.

The passage of substances into the milk appears to have gone relatively unexplored, although its importance has been emphasized by Burn (25) in relation to drug excretion by this route. Since the mammary gland is an organ of highly specialized syntheses, as well as excretion, such studies hold promise of considerable theoretical significance. Thus McConnell (129) found that radioselenium injected as an inorganic salt appeared as organoselenium in the milk.

Lactation.—Considerable interest has been shown in the several constituents of colostrum. In cattle, the nonfatty portion of colostrum supported life in calves better than the crude or clarified fatty portion (7). The Tiselius pattern for cow colostrum was quite

different from that of milk or whey, showing that the difference in protein composition between milk and colostrum was not due simply to an increased percentage of whey components in the former (80). Colostrum feeding led to an increase in blood serum gamma globulins in lambs (31) and calves (89). The wheys of horse, goat, sheep, pig, and cow, but not of human, showed, in electrophoretic studies, a high component associated with antibody proteins (45). The role of immune proteins of bovine milk and colostrum was reviewed by Smith (181).

Lactation was the function most affected in attempts to maintain rats on purified diets (59, 139). Pteroylglutamic acid was one of the factors implicated, and evidently this, together with other unidentified factors, is normally supplied by the colostrum or milk to the young of the pig (27), mouse (135), and rat (64, 140).

Estrogens, Natural and Synthetic

Biology of estrogens.—In *in vitro* studies by Bischoff & Katherman (16) the distribution of estradiol in blood was found to be determined solely by forces governing its solubility in plasma and red cells, to which it is permeable. Nevertheless, Szego & Roberts (190) have postulated estroprotein combinations, based on the coprecipitation of part of the blood estrogens with protein. Bird *et al.* (15) found that estrogens accumulated in the oil of adipose, and in fat infiltrated tissues of birds, a phenomenon that does not appear to have received any attention in mammals. Stilbestrol, dienestrol diacetate, and other synthetic estrogens were used in this study. Hooker *et al.* (102) showed that the liver of the monkey failed to inactivate estrone and estradiol *in vivo*, but this was viewed in terms of a relative inefficiency as compared with the rat.

The mechanism of α-estradiol inactivation in the rat liver *in vitro* appeared to involve a dehydrogenation, but other details were disputed, in a system that is receiving close study (44, 121). In addition to α- and β-estradiol, Westerfield's lactone acetate and estrolactone acetate were inactivated in rat liver *in vivo* while two doisynolic compounds were potentiated (177). Dimethyl-ethyl allenolic acid, which has an estrogenic action in the pregnant and parturient guinea pig, was not destroyed by the liver (41). In the rat, the mode of administration determined the fate of some estrogens, since stilbestrol and dienestrol *per os* were not inacti-

vated, while estrone, estradiol, and hexestrol *per os* were inactivated and estriol was inactivated whether given orally or parenterally (141).

Metabolic pathways.—Stimmel (187) found that single therapeutic doses of natural estrogens in man were metabolized, qualitatively at least, like massive doses. Interconversions of estradiol, estrone, and estriol proceeded much the same in absence of the ovary and uterus, and only a fraction of the injected material was recovered. Dodgson *et al.* (47) found in the rabbit that the synthetic estrogens, stilbestrol and hexestrol, appeared as urinary glucuronides, while dienestrol given orally was excreted largely unchanged in the feces. According to Wilder Smith (199), stilbestrol and hexestrol administered to man were excreted 50 per cent as monoglucuronide and up to 6 per cent as sulfate, while less than 1 per cent was excreted unbound. The major estrogen of pregnant cow bile was shown to be estrone (145). Concerning the site of glucuronic acid conjugation, an ingenious experiment of Schmid (176) indicated that the liver was not essential.

Reproduction in the Male

Male germ cells and hyaluronidase.—With intensive studies continuing, not all the evidence points to the necessity of hyaluronidase as a disperser of the cumulus oophorus preparatory to fertilization. Leonard *et al.* (119) showed that fertilization in the rat occurred before mass displacement of the surrounding follicular cells; these tubal masses were untouched by hyaluronidase introduced into the uterus, but were rapidly denuded by uterine fluid *in vitro*. Swyer (189) found that rabbit eggs were freed from the cumulus, but not from the corona radiata cells, by hyaluronidase, *in vitro*, but introduction of such previously exposed eggs into the tubes of living animals completed the denudation. Since both cumulus and corona resisted the action of tubal extracts a mechanical explanation was advanced. Chang (30), working with rabbits and using minimal effective sperm densities, showed that the addition of hyaluronidase alone did not affect the fertilizing capacity, that normal semen supernatants with added hyaluronidase caused a nonsignificant increase, and that vasectomized buck semen, devoid of hyaluronidase, increased the fertilizing capacity significantly. While authors agree that hyaluronidase is definitely attached to sperm, the conditions of its release are debated. Swyer

(188) found three quarters of the total semen activity to be associated with sperm cells, which were believed to liberate the enzyme progressively to surrounding fluids, but not actively to produce it. Perlman *et al.* (150) kept rat sperm recovered from the uterus under various adverse conditions, incubated at 37°C., frozen, and toluene treated, and found an increase with time in the enzyme level, while the sperm themselves became less motile. Hechter & Hadidian (95) by successive washings in saline of rabbit sperm found hyaluronidase to be constantly renewed until the seventh washing when activity fell sharply. This experiment was interpreted as indicating synthesis of the enzyme by sperm. The potentialities of sperm exhausted of hyaluronidase are not known, but it was evident that when human semen was mixed with five volumes of Ringer solution, centrifuged, and resuspended in its original volume of saline the sperm lost none of their ability to penetrate mucus, in experiments of Pommerenke & Viergiver (154). Leonard *et al.* (120) found that the hyaluronidase levels of rat testis decreased to about the same extent thirty days after hypophysectomy or cryptorchidectomy and were correlated directly with the state of the germinal epithelium both in these animals and in a series of normal animals studied between twenty and ninety days. Sherber *et al.* (178), from the same laboratory, showed that aspermic preparations diffused in skin, although they were inactive viscosimetrically on hyaluronic acid. The authors suggested the presence either of other spreading factors, or of amounts of hyaluronidase too small to be recognized by this technique.

Effect of environmental conditions on sperm.—Rabbit semen had a pH of 7.0 to 8.2 (mean 7.6) and sperm were more sensitive to acid (pH 5.8) than alkali (pH 9.5 to 10). With increasing pH, sperm became more sensitive to hypertonic solutions and around the optimal pH of 7.0 to 8.7, both hyper- and hypotonic solutions were equally deleterious. Complex variations arose from changing either the salt or the glucose concentration of the medium (53, 54). Human sperm were somewhat resistant to arbitrary changes in the tonicity of the medium (124). No very favorable results followed the addition to semen of sulfanilamide (46, 173) or sulfathiazole (46). Amounts of two hundred and fifty to one thousand Oxford Units of penicillin and up to 1,000 μg. of streptomycin per ml. of diluted semen retarded bacterial growth without reducing

livability of sperm. Higher levels were definitely deleterious to motility, while effects on fertility are not yet reported (3, 4). Reed & Reed (163) and Sanders (174) described structural details of human spermatozoa, from electron microscopic observations.

Seminal vesicles and prostate gland.—Emmens & Parkes (55) reviewed the effects of exogenous estrogens on the accessories of male mammals. Krichesky & Benjamin (116) found that estrogens caused reversible atrophy of intraocular prostatic implants in intact rabbits. After atrophy had occurred in castrated hosts, fibrous and muscular tissues were stimulated to hypertrophy, a finding that agrees essentially with results on the gland *in situ*. Horning (103) considers the Golgi apparatus of the mouse prostatic epithelium to be a precise indicator of estrogenic stimulation.

The Hypophysis

Hypophysectomy.—Jost (106) used rabbit embryos decapitated at nineteen, twenty-one, and twenty-two days and surviving till term (twenty-eight days), and Wells (198) fetal rats similarly operated and surviving twenty-eight to one hundred and two hours before severance of the cords near term. In the former, certain anomalies of the genital tract were noted, but growth was not interfered with. In the latter, the volume of the male reproductive glands equalled that of controls.

Histochemistry of pituitary gland.—Abolins (2) found that alkaline phosphatase in the anterior pituitary of the guinea pig was rather closely restricted to acidophil cells, where it was present in the nucleus and at the cell surface; when present in the cytoplasm it seemed to be concentrated in the region of the nucleus and of the Golgi apparatus.

Pituitary hormones.—Hitherto unpublished physicochemical and chemical data on pituitary interstitial cell stimulating hormone and prolactin were given in a review by Evans (56). This author condemned the use of the term pituitary luteotrophin and explicitly stated that maintenance of corpora lutea was a function of the purest lactogenic hormone preparations [see (126)].

The pituitary-gonad relationship.—The concept that the seminiferous tubules are normally supported by androgen seems to be well established. Several years back, studies by Pencharz (148) and by Williams (200) showed that estrogens prevented ovarian atrophy and potentiated the action of gonadotrophins in hypophy-

sectomized rats. Results bearing on these relationships have now been obtained using the intrasplenic ovarian graft preparation. In the rat, Heller & Jungck (96) found that estrogens suppressed the expected weight increase in ovaries so transplanted, and this was adduced in support of a thesis that in the presence of adequate amounts of pituitary secretion, ovarian activity is controlled largely by the level of circulating estrogens. However, in the guinea pig, Lipschutz *et al.* (122) were able to control the heavy lutein and blood follicle formations only by estrogen in combination with progesterone, and the locus of action was placed in the pituitary gland. The question seems to arise how far the splenic transplant system may be regarded as a simple model of estrogen release of either the pituitary or the ovary. Since ovaries so transplanted go on to develop luteomata, caution seems desirable in the application of these results to normal reproductive physiology. Some further evidence was given by Junck *et al.* (108) that pituitary hormones suffer inactivation in the gonads. From the work of Bradbury (19), physiological amounts of estrogen do not suppress the pituitary but, on the contrary, release pituitary hormone to the blood stream. It was indicated, however, that the ovary may be a more potent regulator of pituitary function than are the crystalline estrogens.

The hypothesis was advanced by Tepperman & Tepperman (194) that gonadotrophins affect androgen production in the male rat by a direct involvement in the metabolism of esterified cholesterol. In the work of Claesson & Hillarp (33) already referred to, administration of gonadotrophin to the rat mobilized in the ovary an estrogen precursor believed to be cholesterol.

Gonadotrophins, pregnancy tests.—With the introduction of the ovarian hypermeia test for pregnancy, the vascular aspect of pituitary action on the ovary is receiving some attention. Bradbury (20) described the formation of a rich perifollicular vascular network in the rat ovary forty-eight to seventy-two hours after administering pregnancy gonadotrophin. Rakoff & Fried (160) obtained a strong synergistic effect on ovarian hyperemia in the rat when chorionic gonadotrophin was given in conjunction with quite small amounts of a "pituitary synergist" said to be mostly follicle stimulating hormone. This agrees with the findings of Zondek & Sulman (204). It is possible that investigation of the hyperemia reaction as a phenomenon per se, and the related study

of how hormones affect the ovarian connective tissue, may help to resolve outstanding problems concerning (*a*) steroid effects on the ovary and (*b*) multiple gonadotrophic effects.

Meanwhile the clinical use of the hyperemia test appears to have established its value as an ancillary to the slower but more accurate Aschheim-Zondek and Friedman tests (23, 68, 166). It has also been used in equid pregnancy diagnosis (196, 205). The literature on effects of the gonadotrophic hormones on ovulation and spermatogenesis in amphibians in relation to pregnancy diagnosis was surveyed by Mello (131). The diagnostic reaction of Galli-Mainini (71), employing the appearance in the urine of sperm after injection of pregnancy urine into the male toad, has been extensively studied in South America and elsewhere. The original reaction called for the use of *Bufo arenarum*, indigenous to Uruguay and the Argentine (71, 156), but it now appears that other amphibia react similarly: *Xenopus laevis* (70, 168), Brazilian frogs and toads (131), and the common *Rana temporaria* and *R. esculenta* (101), and *R. pipiens* (169) of North America or Europe.

Antigonadotrophins.—By administering chorionic gonadotrophin mixed with colloidal alumina to rabbits, antigonadotrophic sera that produced specific precipitates with the antigen were obtained by Bussard & Grabar (26); these precipitates may contain excess antibody or excess antigen and no essential difference was seen between these phenomena and the classical neutralization reactions. Some studies of Freud & Uyldert (67) and of Katzman *et al.* (113) confirm the older observations of Thompson on augmenting sera.

Hypothalamo-hypophyseal nervous and vascular link.—Harris (91) described the innervation of the neurohypophysis in the rabbit. He concluded that in the rabbit, rat, guinea pig, cat, dog, monkey, and man it is the function of the pars tuberalis to transmit an anatomic vascular pathway from the neurohypophysis to the pars distalis (90). Similar relations were obtained in amphibia by Green (76). These authors (77) suggested that nerve fibers from the hypothalamico-hypophyseal tract end at capillary loops in the pars tuberalis, whence a humoral link, the hypophysial-portal system, takes origin to subserve the pars distalis. The adrenergic nature of such a link was shown by Markee *et al.* (125, 126). Confirmatory evidence was the inhibition of ovulation in the rabbit when the adrenergic-blocking drug, dibenamine, was given intra-

venously within a minute after copulation. Time relations were such that a three minute delay permitted ovulation to occur (175). Following estrogen administration to pregnant rats, an adrenergic stimulus, which can be blocked by dibenamine, passes to the adenohypophysis after a delay of at least eighteen hours (57).

Animal Breeding and Ecology

The limitations imposed by the environment on possibilities of genic selection were emphasized by Hammond (88) in a review which forms a valuable background for the consideration of a variety of situations. It was shown that most commercially valuable characters were quantitative in nature, and that removal of certain environmental limitations might be necessary to permit further selection to be made. Asdell (8) discussed the future of animal breeding in a popular article.

In Maryland, Phillips (152) found the average service per pregnancy to be 1.4 for the Karakul sheep, and 2.5 or more for other breeds, and the superiority of the first was attributed to adaptation to the hot environmental temperature that precedes the breeding season. The seasonal variation in day length is the chief controlling factor in the breeding season of sheep in England, according to Yeates (202), and in the fertility level of cattle in New York State, according to Mercier & Salisbury (133). Burkhardt (24) hastened the onset of estrus in mares by general irradia- with strong artificial light.

Cole & Casady (38) studied prolificacy in two strains of rats bearing, respectively, 8.9 and 6.5 young per birth and found that the gonadotrophin and thyrotrophin content of the pituitaries of these strains were not demonstrably different. Recently the concept of reproductive wastage has come to the fore. In wild rabbit populations, Brambell & Mills (21) showed that not more than 3.6 per cent of litters were totally lost, but that 36.5 per cent of litters surviving implantation suffered some loss of ova. Greenhill (78) stated that in man the fetal and neonatal death rate was high all over the world for fetuses that had reached a stage of viability. In women known to be fertile, the fetal survival index was placed by Rock & Hertig (171) at 25 per cent at the stage of fertilization. In a study by Drillien (49) of eight thousand births in Edinburgh, 1943–1945, the outcome of a pregnancy (death, stillbirth, or survival) was found to be closely related to the weight at birth.

Secondary Sex Attributes

In this section will be considered a group of organs and some phenomena, either falling into the secondary sexual category or related to sex more remotely. Hamilton (87) mentions the hair as subject to androgenic control and has described the normal appearance of terminal (coarse) hairs in the external ear of males only. Also affected by androgens are: sebaceous glands, skin melanoblasts, muscle fibers of the panniculus, fibrils of dermal collagenous tissue, and mast cells of the dermis (86). From the work of Coujard (40) the anal scent glands of rabbits are ambosexual, and equally sensitive to follicular and androgenic hormones, while the inguinal glands react differentially. Ebling (52) found that testosterone propionate increased the activity of sebaceous glands of the female rat, while ostradiol-benzoate caused atrophy. The inguinal sebaceous glands of the guinea pig were greatly enlarged with anterior pituitary extract (180). Olfactory sensitivity to the lactone of the acid oxy-14-tetradecam-carboxylic-1, a synthetic macrocyclic compound with the odor of musk, prepared by Ruzicka, was shown to be linked to the presence of estrogen, in a remarkable report by Le Magnen (118). Boys, girls, men, and women at menstruation were relatively anosmic to the compound. In the course of the menstrual cycle, many women reacted to it with increasing intensity so that seven to nine days before the next menses it was appreciated violently. Mussio-Fournier *et al.* (138) found that pigmentation of the mammary areolae was increased by the local action of estrogen. Even the submaxillary gland responded to castration and showed sexual dimorphism, according to Raynaud (162). Antler growth in the male Virginia deer is under the complex control of an extra gonadal system, probably the anterior pituitary gland, from the studies of Wislocki *et al.* (201). Male hormone was responsible for the initial priming of the mechanism and for the secondary hardening (calcification) and shedding of the velvet. Ovariectomized female deer grew antlers under androgen stimulation.

Enzymes and Reproductive Control

While it has become a truism that hormonal actions will eventually find their proximate explanation in appropriate enzyme systems, the outlines of such control are still dim and studies are largely of an *ad hoc* character. Enzyme studies in uterus and pi-

tuitary gland have already been dealt with. Acid and alkaline phosphatase were studied by Stafford *et al.* (185) in ovarian tissues of the rat in pregnancy and lactation using tissue homogenates, and concurrently alkaline phosphatase was followed histochemically by Talbert *et al.* (191). Succinic dehydrogenase appeared to follow a similar time course, marked by a sharp midpregnancy rise in the corpora lutea, and by a rise to even higher levels in the corpora of lactation (134). Steroid hormones in relation to the hydrolytic enzymes were reviewed by Kochakian (115). A new concept of the metabolic conjugation of estrogens with glucuronic acid as a prerequisite for their utilization was suggested by Fishman (61).

A group of enzymes that includes the spreading factors and hyaluronidases has been considered to play a role in certain phases of reproduction; such a function of the mammalian spreading factors was mentioned by Duran-Reynals (51) and the possible function of hyaluronidase in fertilization has been actively investigated. The substrates of these enzymes are: intra- or extracellular mucopolysaccharides, ground substance, basement membranes, glycoprotein membranes, and connective tissue, including cartilage. Other possible roles of such enzyme systems have been indicated at appropriate places in this review.

Reviews and Books

Certain topics not touched on in this review have received ample treatment elsewhere. Such are: androgen metabolism, by Dorfman (48); the use of androgens in males, by Heller & Maddock (97); and in women by Carter *et al.* (29); local actions of sex hormones, by Speert (184); spectrophotometric methods for estrogens, by Friedgood & Garst (69); and for sterol hormones, by Jones (105); reproductive epithelia, by Papanicolaou *et al.* (144); sex hormone deficiencies, by McCullagh (130); sexual behavior, by Kinsey *et al.* (114), and by Beach (12); B-vitamins in relation to estrogens, by Hertz (98); hormonal control of sexual differentiation, by Jost (107).

LITERATURE CITED

1. Abarbanel, A. R., *Western J. Surg. Obstet. Gynecol.*, **56**, 26–34 (1948)
2. Abolins, L., *Nature*, **161**, 556–57 (1948)
3. Almquist, J. O., Thorp, W. T. S., and Knodt, C. B., *J. Dairy Sci.*, **31**, 11–19 (1948)

4. ALMQUIST, J. O., THORP, W. T. S., AND GLANTZ, P. J., *J. Dairy Sci.*, **31**, 542–43 (1948)
5. AMOROSO, E. C., HANCOCK, J. L., AND ROWLANDS, I. W., *Nature*, **161**, 355–56 (1948)
6. ARZAC, J. P., AND BLANCHET, E., *J. Clin. Endocrinol.*, **8**, 315–24 (1948)
7. ASCHAFFENBURG, R., BARTLETT, S., KON, S. K., TERRY, P., THOMPSON, S. Y., AND WALKER, D. M., *Biochem. J.*, **42**, xxx (1948)
8. ASDELL, S. A., *Sci. Monthly*, **64**, 477–80 (1947)
9. ATKINSON, W. B., AND ENGLE, E. T., *Endocrinology*, **40**, 327–33 (1947)
10. ATKINSON, W. B., SHETTLES, L. B., AND ENGLE, E. T., *Anat. Record*, **100**, 637 (1948)
11. BASSETT, D. L., *Anat. Record*, **100**, 731–32 (1948)
12. BEACH, F. A., *Physiol. Revs.*, **27**, 240–307 (1947)
13. BENDER, S., *J. Obstet. Gynaecol. Brit. Empire*, **54**, 783–92 (1947)
14. BENSLEY, C. M., *Anat. Record*, **100**, 732–33 (1948)
15. BIRD, S., PUGSLEY, L. I., AND KLOTZ, M. O., *Endocrinology*, **41**, 282–94 (1947)
16. BISCHOFF, F., AND KATHERMAN, R. E., *Am. J. Physiol.*, **152**, 189–96 (1948)
17. BISSETT, N. G., BROOKSBANK, B. W. L., AND HASLEWOOD, G. A. D., *Biochem. J.*, **42**, 366–71 (1948)
18. BOYARSKY, L. H., BAYLIES, H., CASIDA, L. E., AND MEYER, R. K., *Endocrinology*, **41**, 312–21 (1947)
19. BRADBURY, J. T., *Endocrinology*, **41**, 501–13 (1947)
20. BRADBURY, J. T., *Anat. Record*, **100**, 642–43 (1948)
21. BRAMBELL, F. W. R., AND MILLS, I. H., *J. Exptl. Biol.*, **24**, 192–210 (1947)
22. *Brit. Med. Bull.*, **5**(2–3), Part I, 119–220 (1947)
23. BUNDE, C. A., *Am. J. Obstet. Gynecol.*, **53**, 317–20 (1947)
24. BURKHARDT, J., *J. Agr. Sci.*, **37**, 64–68 (1947)
25. BURN, J. H., *Brit. Med. Bull.*, **5** (2–3), 1113 (1947)
26. BUSSARD, A., AND GRABAR, P., *Bull. soc. chim. biol.*, **29**, 195–211 (1947)
27. BUSTAD, L. K., HAM, W. E., AND CUNHA, T. J., *Arch Biochem.*, **17**, 249–60 (1948)
28. BUTCHER, E. O., *Anat. Record*, **98**, 547–56 (1947)
29. CARTER, A. C., COHEN, E. J., AND SHORR, E., *Vitamins & Hormones*, **5**, 318–91 (1947)
30. CHANG, M. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 51–54 (1947)
31. CHARLWOOD, P. A., AND THOMSON, A., *Nature*, **161**, 59 (1948)
32. CLAESSON, L., AND HILLARP, N-Å., *Acta Physiol. Scand.*, **13**, 115–29 (1947)
33. CLAESSON, L., AND HILLARP, N-Å., *Acta Physiol. Scand.*, **14**, 102–19 (1947)
34. CLAESSON, L., AND HILLARP, N-Å., *Acta Anat.*, **3**, 109–14 (1947)
35. CLAESSON, L., *Acta Anat.*, **3**, 295–311 (1947)
36. CLARK, G., *Endocrinology*, **41**, 327–29 (1947)
37. COLE, H. H. (Personal communication, 1948)
38. COLE, H. H., AND CASADY, R. B., *Endocrinology*, **41**, 119–26 (1947)
39. COLE, H. H., HOWELL, C. E., AND HART, G. H., *Anat. Record*, **49**, 199–209 (1931)
40. COUJARD, R., *Rev. can. biol.*, **6**, 3–25 (1947)
41. COURRIER, R., HOREAU, A., AND JACQUES, J., *Compt. rend. soc. biol.*, **141**, 747–48 (1947)

42. DAVIS, M. E., AND FUGO, N. W., *Proc. Soc. Exptl. Biol. Med.*, **65**, 283–89 (1947)
43. DAVIS, M. E., AND FUGO, N. W., *Proc. Soc. Exptl. Biol. Med.*, **66**, 39–42 (1947)
44. DE MEIO, R. H., RAKOFF, A. E., CANTAROW, A., AND PASCHKIS, K. E., *Federation Proc.*, **7**, 27 (1948)
45. DEUTSCH, H. F., *J. Biol. Chem.*, **169**, 437–48 (1947)
46. DIMITROPOULOS, E., NENNAUX, L., AND CORDIEZ, E., *Compt. rend. soc. biol.*, **141**, 1283–86 (1947)
47. DODGSON, K. S., GARTON, G. A., STUBBS, A. L., AND WILLIAMS, R. T., *Biochem. J.*, **42**, 357–65 (1948)
48. DORFMAN, R. I., *Recent Progress in Hormone Research*, **2**, 179–206 (1948)
49. DRILLIEN, C. M., *J. Obstet. Gynaecol. Brit. Empire*, **54**, 300–23 (1947)
50. DUKE, K. L., *Anat. Record*, **98**, 507–20 (1947)
51. DURAN-REYNALS, F., *Bact. Revs.*, **6**, 197–252 (1942)
52. EBLING, F. J., *J. Endocrinol.*, **5**, lxxxix–xc (1948)
53. EMMENS, C. W., *J. Physiol. (London)*, **106**, 471–81 (1947)
54. EMMENS, C. W., *J. Physiol. (London)*, **107**, 129–40 (1948)
55. EMMENS, C. W., AND PARKES, A. S., *Vitamins & Hormones*, **5**, 233–72 (1947)
56. EVANS, H. M., *J. physiologie et path. gén.*, **39**, 121–36 (1947)
57. EVERETT, J. W., SAWYER, C. H., AND MARKEE, J. E., *Anat. Record*, **100**, 740 (1948)
58. EVERETT, N. B., AND HENDERSON, J. E., *Anat. Record*, **100**, 658 (1948)
59. FENTON, P. F., AND COWGILL, G. R., *J. Nutrition*, **33**, 703–12 (1947)
60. FERIN, J., *Ann. endocrinol. (Paris)*, **8**, 171–76 (1947)
61. FISHMAN, W. H., *J. Biol. Chem.*, **169**, 7–15 (1947)
62. FLEXNER, L. B., VOSBURGH, G. J., AND COWIE, D. B., *Anat. Record*, **100**, 661 (1948)
63. FLEXNER, L. B., COWIE, D. B., HELLMAN, L. M., WILDE, W. S., AND VOSBURGH, G. J., *Am. J. Obstet. Gynecol.*, **55**, 469–80 (1948)
64. FOLLEY, S. J., HENRY, K. M., AND KON, S. K., *Brit. J. Nutrition*, **1**, 39–52 (1947)
65. FOLLEY, S. J., AND GREENBAUM, A. L., *J. Endocrinol.*, **5**, 236–42 (1948)
66. FORBES, T. R., *Anat. Record*, **100**, 661–62 (1948)
67. FREUD, J., AND UYLDERT, I. E., *J. Endocrinol.*, **5**, 59–67 (1947)
68. FRIED, P. H., *Am. J. Obstet. Gynecol.*, **54**, 689–93 (1947)
69. FRIEDGOOD, H. B., AND GARST, J. B., *Recent Progress in Hormone Research*, **2**, 31–78 (1948)
70. GALLIEN, L., *Compt. rend.*, **226**, 1141–43 (1948)
71. GALLI-MAININI, C., *Semana méd. (Buenos Aires)*, **54**, 447–54 (1947)
72. GILBERT, C., AND GILLMAN, J., *S. African J. Med. Sci.*, **12**, 77–85 (1947)
73. GILLMAN, J., AND GILBERT, C., *S. African J. Med. Sci.*, **12**, 87–97 (1947)
74. GODET, R., *Compt. rend.*, **226**, 1748–49 (1948)
75. GOMORI, G., *Proc. Soc. Exptl. Biol. Med.*, **51**, 133–34 (1942)
76. GREEN, J. D., *Anat. Record*, **99**, 21–53 (1947)
77. GREEN, J. D., AND HARRIS, G. W., *J. Endocrinol.*, **5**, 136–46 (1947)
78. GREENHILL, J. P., *J. Obstet. Gynaecol. Brit. Empire*, **54**, 577–91 (1947)

79. GROLLMAN, A., *Am. J. Physiol.*, **151**, 373–79 (1947)
80. GRÖNWALL, A., *Nature*, **159**, 376 (1947)
81. GURCHOT, C., KREBS, E. T., JR., AND KREBS, E. T., *Surg., Gynecol. Obstet.*, **84**, 301–12 (1947)
82. GUTERMAN, H. S., AND SCHROEDER, M. S., *J. Lab. Clin. Med.*, **33**, 356–66 (1948)
83. HALL, K., *J. Endocrinol.*, **5**, 174–82 (1947)
84. HALL, K., AND NEWTON, W. H., *J. Physiol. (London)*, **106**, 18–27 (1947)
85. HAMILTON, C. E., *Anat. Record*, **97**, 47–62 (1947)
86. HAMILTON, J. B., *Anat. Record*, **97**, 340 (1947)
87. HAMILTON, J. B., *Endocrinology*, **40**, 454 (1947)
88. HAMMOND, J., *Biol. Revs. Cambridge Phil. Soc.*, **22**, 195–214 (1947)
89. HANSEN, R. G., AND PHILLIPS, P. H., *J. Biol. Chem.*, **171**, 223–27 (1947)
90. HARRIS, G. W., *J. Anat.*, **81**, 343–51 (1947)
91. HARRIS, G. W., *Trans. Roy. Soc. (London)* [B]**232**, 385–441 (1947)
92. HARRIS, M., AND EAKIN, R. M., *Anat. Record*, **100**, 40 (1948)
93. HARRISON, R. J., *J. Anat.*, **82**, 21–48 (1948)
94. HARTER, B. T., *Anat. Record*, **100**, 672 (1948)
95. HECHTER, O., AND HADIDIAN, Z., *Endocrinology*, **41**, 204–5 (1947)
96. HELLER, C. G., AND JUNGCK, E. C., *Proc. Soc. Exptl. Biol. Med.*, **65**, 152–54 (1947)
97. HELLER, C. G., AND MADDOCK, W. O., *Vitamins & Hormones*, **5**, 394–432 (1947)
98. HERTZ, R., *Recent Progress in Hormone Research*, **2**, 161–77 (1948)
99. HILL, R. T., *Endocrinology*, **42**, 339–51 (1948)
100. HILL, R. T., *Anat. Record*, **100**, 674–75 (1948)
101. HINGLAIS, H., AND HINGLAIS, M., *Compt. rend.*, **226**, 1041–43 (1948)
102. HOOKER, C. W., DRILL, V. A., AND PFEIFFER, C. A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 192–94 (1947)
103. HORNING, E. S., *Quart. J. Microscop. Sci.*, **88**, 45–53 (1947)
104. HUBER, D., *Biochem. J.*, **41**, 609–11 (1947)
105. JONES, R. N., *Recent Progress in Hormone Research*, **2**, 3–29 (1948)
106. JOST, A., *Compt. rend.*, **225**, 322–24 (1947)
107. JOST, A., *Biol. Revs. Cambridge Phil. Soc.*, **23**, 201–36 (1948)
108. JUNGCK, E. C., HELLER, C. G., AND NELSON, W. O., *Proc. Soc. Exptl. Biol. Med.*, **65**, 148–52 (1947)
109. KAISER, I. H., *Anat. Record*, **99**, 199–225 (1947)
110. KAISER, I. H., *Anat. Record*, **99**, 353–68 (1947)
111. KAISER, I. H., *Bull. Johns Hopkins Hosp.*, **82**, 429–45 (1948)
112. KAMELL, S. A., AND ATKINSON, W. B., *Proc. Soc. Exptl. Biol. Med.*, **67**, 415–16 (1948)
113. KATZMAN, P. A., WADE, N. J., AND DOISY, E. A., *Endocrinology*, **41**, 27–34 (1947)
114. KINSEY, A. C., POMEROY, W. B., AND MARTIN, C. E., *Sexual Behavior in the Human Male*, 804 pp. (W. B. Saunders Company, Philadelphia and London, 1948)
115. KOCHAKIAN, C. D., *Recent Progress in Hormone Research*, **1**, 177–216 (1947)
116. KRICHESKY, B., AND BENJAMIN, J. A., *J. Urol.*, **58**, 114–24 (1947)

117. LaVelle, F. W., *Anat. Record*, **100**, 750 (1948)
118. Le Magnen, J., *Compt. rend.*, **226**, 694–95 (1948)
119. Leonard, S. L., Perlman, P. L., and Kurzrok, R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 517–18 (1947)
120. Leonard, S. L., Perlman, P. L., and Kurzrok, R., *Endocrinology*, **42**, 176–80 (1948)
121. Levy, H., *Arch. Biochem.*, **14**, 325–34 (1947)
122. Lipschutz, A., Iglesias, R., Bruzzone, S., Humerez, J., and Peñaranda, J. M., *Endocrinology*, **42**, 201–9 (1948)
123. Mack, H. C., and Parks, A. E., *J. Clin. Endocrinol.*, **7**, 351–63 (1947)
124. MacLeod, J., *Anat. Record*, **100**, 694 (1948)
125. Markee, J. E., Sawyer, C. H., and Hollinshead, W. H., *Anat. Record*, **97**, 398 (1947)
126. Markee, J. E., Sawyer, C. H., and Hollinshead, W. H., *Recent Progress in Hormone Research*, **2**, 117–31 (1948)
127. Marvin, H. N., *Anat. Record*, **100**, 694–95 (1948)
128. Matthews, L. H., *Proc. Zool. Soc. London*, **117**, 313–33 (1947)
129. McConnell, K. P., *J. Biol. Chem.*, **173**, 653–57 (1948)
130. McCullagh, E. P., *Recent Progress in Hormone Research*, **2**, 295–344 (1948)
131. Mello, M. I., *Hospital, O (Rio de Janeiro)*, **33**, 57–64 (1948)
132. Menkin, M. F., and Rock, J., *Anat. Record*, **100**, 695–96 (1948)
133. Mercier, E., and Salisbury, G. W., *J. Dairy Sci.*, **30**, 817–26 (1947)
134. Meyer, R. K., Soukup, S. W., McShan, W. H., and Biddulph, C., *Endocrinology*, **41**, 35–44 (1947)
135. Mirone, L., and Cerecedo, L. R., *Arch. Biochem.*, **15**, 324–26 (1947)
136. Moore, C. R., and Wang, H., *Physiol. Zoöl.*, **20**, 300–21 (1947)
137. Murphree, R. L., Warwick, E. J., Casida, L. E., and McShan, W. H., *Endocrinology*, **41**, 308–11 (1947)
138. Mussio-Fournier, J. C., Cervino, J. M., and Olivieri, E., *Ann. endocrinol. (Paris)*, **8**, 114–16 (1947)
139. Nelson, M. M., and Evans, H. M., *Arch. Biochem.*, **12**, 213–28 (1947)
140. Nelson, M. M., and Evans, H. M., *Arch. Biochem.*, **13**, 265–76 (1947)
141. Nielsen, A. T., Pedersen-Bjergaard, K., and Tønnesen, M., *J. Endocrinol.*, **5**, 111–14 (1947)
142. Odor, D. L., and Blandau, R. J., *Anat. Record*, **97**, 400–1 (1947)
143. Ogston, A. G., Philpot, J. S. L., and Zuckerman, S., *J. Endocrinol.*, **1**, 231–38 (1939)
144. Papanicolaou, G. N., Traut, H. F., and Marchetti, A. A., *The Epithelia of Woman's Reproductive Organs*, 46 pp., Pl. A-K (The Commonwealth Fund, N. Y., 1948)
145. Pearlman, W. H., Rakoff, A. E., Cantarow, A., and Paschkis, K. E., *J. Biol. Chem.*, **170**, 173–79 (1947)
146. Peckham, B. M., and Greene, R. R., *Endocrinology*, **41**, 273–76 (1947)
147. Peckham, B. M., and Greene, R. R., *Endocrinology*, **41**, 277–81 (1947)
148. Pencharz, R. I., *Science*, **91**, 554–55 (1940)
149. Perlman, P. L., and Leonard, S. L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 24–25 (1947)
150. Perlman, P. L., Leonard, S. L., and Kurzrok, R., *Endocrinology*, **42**, 26–30 (1948)

151. PETERSEN, W. E., *Recent Progress in Hormone Research*, **2**, 133–58 (1948)
152. PHILLIPS, R. W., *Intern. Physiol. Congr. Abstracts*, 40–41 (1947)
153. PIGEAUD, H., AND DUBREUIL, P., *Gynécol. et Obstet.*, **46**, 198–200 (1947)
154. POMMERENKE, W. T., AND VIERGIVER, E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 161–63 (1947)
155. POPJÁK, G., *Nature*, **160**, 841–42 (1948)
156. POU DE SANTIAGO, A., *Arch. uruguay. med. cirug. y especial.* (*Montevideo*), **30**, 457–73 (1947)
157. PRICE, D., *Physiol. Zoöl*, **20**, 213–47 (1947)
158. PRITCHARD, J. J., *J. Anat.*, **81**, 352–64 (1947)
159. RABINOVITCH, J., *Nature*, **161**, 605 (1948)
160. RAKOFF, A. E., AND FRIED, P. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 491–92 (1947)
161. RAYNAUD, J., AND RAYNAUD, A., *Ann. endocrinol.* (*Paris*), **8**, 81–86 (1947)
162. RAYNAUD, J., *Ann. endocrinol.* (*Paris*), **8**, 359–62 (1947)
163. REED, C. I., AND REED, B. P., *Anat. Record*, **100**, 1–7 (1948)
164. REYNOLDS, S. R. M., *Ann. Rev. Physiol.*, **10**, 65–92 (1948)
165. RICHTER, K., *Wien med. Wochschr.*, **97**, 281–84 (1947)
166. RILEY, G. M., SMITH, M. H., AND BROWN, P., *J. Clin. Endocrinol.*, **8**, 233–43 (1948)
167. RISMAN, G. C., *J. Morphol.*, **81**, 343–97 (1947)
168. ROBBINS, S. L., PARKER, F., JR., AND BIANCO, P. D., *Endocrinology*, **40**, 227–29 (1947)
169. ROBBINS, S. L., AND PARKER, F., JR., *Endocrinology*, **42**, 237–43 (1948)
170. ROBERTSON, G. G., O'NEILL, S. L., AND CHAPPELL, R. H., *Anat. Record*, **100**, 9–28 (1948)
171. ROCK, J., AND HERTIG, A. T., *Am. J. Obstet. Gynecol.*, **55**, 6–17 (1948)
172. SADOWSKY, A., BRZEZINSKI, A., BROMBERG, Y. M., AND ROSENTHAL, F., *Exptl. Med. and Surg.*, **5**, 259–63 (1947)
173. SALISBURY, G. W., AND KNODT, C. B., *J. Dairy Sci.*, **30**, 361–69 (1947)
174. SANDERS, J. H., *Western J. Surg. Obstet. Gynecol.*, **56**, 306–8 (1948)
175. SAWYER, C. H., MARKEE, J. E., AND HOLLINSHEAD, W. H., *Endocrinology*, **41**, 395–402 (1947)
176. SCHMID, F., *Compt. rend. soc. biol.*, **141**, 909–11 (1947)
177. SEGALOFF, A., *Endocrinology*, **42**, 15–19 (1948)
178. SHERBER, D. A., BIRNBERG, C. H., AND KURZROK, R., *Endocrinology*, **42**, 20–25 (1948)
179. SKOWRON, W., AND ZAJACZEK, S., *Compt. rend. soc. biol.*, **141**, 1105–7 (1947)
180. SMELSER, G. K., *Anat. Record*, **100**, 712 (1948)
181. SMITH, E. L., *J. Dairy Sci.*, **31**, 127–38 (1948)
182. SMITH, G. v. S., AND SMITH, O. W., *Physiol. Revs.*, **28**, 1–22 (1948)
183. SOMMERVILLE, I. F., GOUGH, N., AND MARRIAN, G. F., *J. Endocrinol.*, **5**, 247–57 (1948)
184. SPEERT, H., *Physiol. Revs.*, **28**, 23–50 (1948)
185. STAFFORD, R. A., MCSHAN, W. H., AND MEYER, R. K., *Endocrinology*, **41**, 45–54 (1947)
186. STEWART, H. L., SANO, M. E., AND MONTGOMERY, T. L., *J. Clin. Endocrinol.*, **8**, 175–88 (1948)
187. STIMMEL, B. F., *J. Clin. Endocrinol.*, **7**, 364–73 (1947)

188. SWYER, G. I. M., *Biochem. J.*, **41**, 413–17 (1947)
189. SWYER, G. I. M., *Nature*, **159**, 873–74 (1947)
190. SZEGO, C. M., AND ROBERTS, S., *Endocrinology*, **41**, 322–24 (1947)
191. TALBERT, G. B., STAFFORD, R. A., MEYER, R. K., AND MCSHAN, W. H., *Anat. Record*, **100**, 718 (1948)
192. TALMAGE, R. V. N., *J. Exptl. Zoöl.*, **106**, 281–97 (1947)
193. TALMAGE, R. V. N., *Anat. Record*, **99**, 91–113 (1947)
194. TEPPERMAN, J., AND TEPPERMAN, H. M., *Endocrinology*, **41**, 187–95 (1947)
195. TORPIN, R., *Am. J. Obstet. Gynecol.*, **53**, 78–81 (1947)
196. VALLE, J. R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 352–54 (1947)
197. VAN WAGENEN, G., *Anat. Record*, **100**, 761 (1948)
198. WELLS, L. J., *Anat. Record*, **97**, 409 (1947)
199. WILDER SMITH, A. E., *Nature*, **160**, 787 (1947)
200. WILLIAMS, P. C., *Nature*, **145**, 388–89 (1940)
201. WISLOCKI, G. B., AUB, J. C., AND WALDO, C. M., *Endocrinology*, **40**, 202–24 (1947)
202. YEATES, N. T. M., *Nature*, **160**, 429–30 (1947)
203. ZONDEK, B., *Lancet*, **I**, 178–79 (1947)
204. ZONDEK, B., AND SULMAN, F., *J. Endocrinol.*, **5**, lxxxviii (1948)
205. ZONDEK, B., AND SULMAN, F., *Endocrinology*, **40**, 322–26 (1947)
206. ZONDEK, B., SULMAN, F., AND BLACK, R., *J. Am. Med. Assoc.*, **136**, 965–69 (1948)

METABOLIC FUNCTIONS OF THE ENDOCRINE SYSTEM[1]

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Some concept of the task confronting the reviewer of this active field can be had from the brief statement that over one thousand papers have been studied. It would obviously be inappropriate to claim that the 288 discussed herein were the only significant ones. The selection has been quite arbitrary and most of the discussions painfully brief. The writer makes no apology for omissions, but sincerely hopes that he has not outraged any workers by performing correlations with their results which they would rather have avoided.

Hormonal Effects on Tissues

One of the most important, as well as challenging, recent developments in the field of endocrine research has been the probing into the detailed mechanism of hormonal effects. In the present survey, practically all of such work has been gathered into a section on tissue effects; this was done arbitrarily as much for emphasis as for a logical approach. This line of endeavor follows two general patterns: one, the more fruitful to date, has involved the study of various changes in tissues excised from animals treated with the hormone in question, while the second consists of attempting to show *in vitro* effects of the hormone on various tissue preparations ranging from muscle strips and tissue slices to isolated enzyme preparations. The obvious ultimate goal of all this inquiry is the elucidation of *in vivo* function. It should be pointed out, however, that occasionally the temptation to produce a correlation outstrips the available data on which such a relationship must be based.

Insulin and carbohydrate metabolism.—Probably the most challenging work has been that stemming from the original observation by Price, Cori & Colowick (199) of the inhibition of the

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hexokinase reaction, glucose→glucose-6-phosphate, by anterior pituitary extract (APE) and the removal of this inhibition by insulin. Broh-Kahn & Mirsky (31) reported that the hexokinase inhibiting activity of APE bore no relationship to the diabetogenic potency. These workers found muscle from alloxan-diabetic rats to yield hexokinase preparations fully as active as muscle from normal animals, and insulin added directly to have no effect. Colowick, Cori & Slein (45) showed that the hexokinase activity of diabetic rat muscle extracts could be inhibited 21 to 76 per cent in one half of the instances by adrenal cortical extract, in contrast to no inhibition of preparations from normal rats. Insulin removed this inhibition, but gave no stimulation. The belief was expressed that the inhibitory effect of adrenal cortical extract probably depended upon the presence of anterior pituitary inhibitor in the diabetic muscle, but this is questionable in view of the normal hexokinase activity in diabetic muscle extracts as well as the absence of a direct insulin effect.

Reiss & Rees reported that both adrenalectomy and hypophysectomy increased the hexokinase activity of brain cortex extracts (210). Hypophysectomy was also found to increase anaerobic glycolysis of brain, but had no effect on the Q_{O_2}. The authors' conclusion that the brain, following removal of pituitary or adrenal cortices, "consumes and metabolizes an increased amount of sugar," need not be true—anaerobic glycolysis has not been shown to be an obligatory aspect of *in vivo* brain metabolism.

Other enzyme systems involved in the over-all reaction glucose⇄glycogen in the rat liver have been studied by Broh-Kahn *et al.* in normal and alloxan-diabetic rats (32, 33). No effect of insulin was found on phosphoglucomutase, phosphorylase, the "prosthetic group-removing enzyme" of Cori, or glucose-6-phosphatase. Since insulin exerts a considerable influence on the glucose⇄glycogen cycle in the animal (and, of course in so-called "intact-cell" preparations), these workers stated the belief that insulin acts in the intact cell through mechanisms other than a direct action on enzymes. A contrasting opinion was expressed by Cori (48): pointing out that insulin has its most potent effect on carbohydrate utilization in the animal without pituitary or adrenal glands (a fact which many have ignored when considering this work), he concluded that insulin may have a direct stimulatory effect on some enzyme system not yet studied.

With the preparation and study of a galactokinase (259), one may anticipate a reawakening of interest in the enzymatic details of the metabolism of this interesting monosaccharide.

Many workers interested in renewing the *in vitro* attack on insulin function in muscle have returned to the use of rat diaphragm, initiated by Gemmill in 1941 (97). Corkill & Nelson (49) reported that insulin nearly doubled the glucose utilization, all of which could be accounted for as glycogen. When the animals were injected with APE the glucose utilization without added insulin was normal, but the insulin stimulation amounted to only one fifth of the normal response. If the lack of insulin effect be due to an increased APE inhibition of hexokinase, either this inhibition is not exerted in the absence of added insulin or else the hexokinase activity is not the limiting step in glucose→glycogen it is usually assumed to be. Krahl & Cori (147) noted a considerable increase in glucose utilization with added insulin in diaphragm from normal rats. When severely diabetic rats (alloxanized) were used, glucose utilization was depressed 59 per cent; insulin caused a considerable stimulation but did not return utilization even to the non-insulin normal. Hexokinase activity of skeletal muscle from diabetic rats was normal. Adrenalectomy of severely diabetic animals raised the *in vitro* diaphragm utilization to normal, but now the insulin enhancement was only about 75 per cent of normal.

A highly detailed empirical study of *in vitro* optimum conditions by Stadie & Zapp (239) revealed many discrepancies between oxygen consumption and glycogen synthesis by rat diaphragm as well as between these conditions and those believed to exist *in vivo*. For example, magnesium stimulated glycogenesis between about 0.005 to 0.020 *M*, but with the latter concentration, oxygen consumption was decreased 30 per cent. These workers found a marked insulin effect on glycogenesis, but none on Q_{o_2}. Since this insulin stimulation continued to increase from 0.1 to 1.0 per cent glucose concentration, it appears as though Hector, Levine & Soskin's concept (120) of the inverse relationship between insulin and glucose concentration did not hold under these conditions. Insulin must have a specific effect on glycogenesis, since the same extra amount of glycogen could be synthesized regardless of whether the starting glycogen level was $5\mu M$ or $44\mu M$ per gram of tissue. No evidence could be adduced from a study of organic phosphate levels as to whether the hexokinase reaction is the critical step in glucose→glyclogen,

nor was it possible to settle on a source of the energy required for rephosphorylation of adenosinediphosphate (ADP). Goranson, Hamilton & Haist, in a study of chemical changes during and after trauma of rat hind legs (101), found that insulin increased the turnover of phosphocreatine (PC) and adenosinetriphosphate (ATP) phosphorus without any change in absolute amounts.

Riesser also showed insulin enhancement of glycogenesis in the rat hemidiaphragm (212). Whole adrenal gland extract and epinephrine overcame the insulin effect, whereas adrenal cortical extract, desoxycorticosterone, or pituitary extracts did not. In three experiments on adrenalectomized rats, insulin had a very slight effect. Corkill & Nelson (50) reported that 0.05 per cent fructose added to rat diaphragm in the presence of glucose and insulin caused a still further increase in glucose disappearance and glycogen synthesis.

Stadie, Haugaard & Perlmutter (237) have found extraordinary optimal conditions for *in vitro* glycogenesis by rat heart slices: sodium and potassium both are inhibitors, and isosmolarity is best obtained by the use of sorbitol plus glucose. Addition of insulin yielded variable results. Alloxan-diabetic rat hearts showed marked glycogenolysis, not reversed by insulin. None of this series of useful findings on the heart could be applied to liver to cause satisfactory glycogenesis. These same authors have reopened without outstanding success the question of insulin catalysis of oxidative reactions by studying anew Q_{O_2} and pyruvate utilization by various pigeon breast, rat and human muscle preparations (238). Bloch & Kramer (27) have found that insulin catalyzes the incorporation of acetic acid carboxyl group carbon into fatty acids by liver slices under proper conditions.

Sutherland & Cori (247) have given the details of the finding, startling when first reported, of a substance causing liver glycogenolysis *in vivo* or *in vitro* present in the supposedly highly purified (even crystalline) American insulins but removed at the final stage of recrystallization of the Danish insulin. The glycogenolytic factor could be removed as a contaminating protein from insulin, or the insulin could be inactivated with cysteine or alkali, leaving the new factor unaltered. The authors believe the material acts on the phosphorylase step of glycogenolysis. The possibility that this may represent a genuine hormonal secretion of the pancreas, probably of the α-cells of the islets of Langerhans, is emphasized by the re-

port of Heard *et al.* on such a preparation (119). This reviewer feels doubtful that the "contra-insulin" of DeWaele (61), obtained by a fat-solvent extraction of pancreas, can be as seriously entertained.

Epinephrine injection in the rat was found by Cohen (44) to cause considerable inhibition of anaerobic glycolysis of the diaphragm removed 40 to 60 min. later from the animal, through release of some material from the pituitary.

Hormonal effects on phosphatases and arginase.—Many studies have been carried out on acid and alkaline phosphatase activity of various tissues, measured either chemically, allowing greater accuracy, or histochemically, permitting a more exact localization of the enzyme. At the present time, it is difficult to fit measurements made on such artificial substrates as β-glycerophosphate, phenol phosphate, phenolphthalein phosphate, etc., into any recognized scheme of phosphorylations or dephosphorylations. Until some correlation is achieved with definite enzyme systems or specific chemical changes, attributing any particular physiological function to a "phosphatase" must be considered premature. An excellent survey of the function of phosphate in biological systems has been carried out by Kalckar (137).

Although Bunting (38) found no change in alkaline phosphatase in the kidney of hyperglycemic rats, Marsh & Drabkin (170) reported increased kidney acid and alkaline phosphatase activities and decreases resulting from phlorhizinization. These changes were histologically localized in the renal tubules. On the synthesis side, it was reported that the active phosphorylation of glucose shown by the fasted animal was actually reversed in alimentary hyperglycemia. These authors suggested that renal tubular reabsorption of glucose depends upon the level to which the phosphatase activity can be raised; beyond this limit, reabsorption is incomplete and glycosuria results. However, this concept does not provide for or identify the glucose phosphate ester upon which the tubular cell phosphatase presumably acts. What would be gained by phosphorylation and dephosphorylation of the transfer substrate, either in intestinal absorption or renal tubular reabsorption? Ponz (198) noted increased alkaline phosphatase activity in the upper and middle small intestine following three days of thyroxine injections in the rat. Verne & Hébert found (266) that the complete disappearance of alkaline phosphatase along the intestine following

adrenalectomy could be reversed by injections of adrenal cortical extract (ACE) or reimplantation of one adrenal. If such observations can consistently be correlated with the various endocrine factors claimed to influence intestinal absorption (233), the riddle posed above would be closer to solution.

A stimulating report of work by Kerppola, of Helsinki, was given in a review of progress in diabetes by Joslin *et al.* (136). Intravenous injection of purified alkaline phosphatase into fasting rabbits elevated the blood sugar; continued injections lowered the glucose tolerance and decreased the response to insulin. Burgen & Lorch (39) found that alloxan and other diabetogenic ureides inhibited the alkaline phosphatase in hog kidney, but kidneys from cats and rabbits treated with alloxan showed no change histochemically, although Bunting reported some decrease measured chemically (38). In the pancreas, the degenerated islets showed less than the normal phosphatase reaction. As the diabetic state became established after the injection of alloxan, a considerable increase was noted in liver acid and alkaline phosphatases (64) and in serum alkaline phosphastase (41). With good control of the diabetes, the phosphatases returned to normal.

Kochakian & Vail obtained decreases in liver and kidney arginase and alkaline phosphatase activities after adrenalectomy in the rat (146, 262). Treatment of these animals with ACE increased both liver phosphatase and glycogen, while desoxycorticosterone acetate (DOCA) had no effect. Marked enhancement of both kidney enzyme activities resulted from testosterone injection. In addition Elftman (68) has reported appearance of alkaline phosphatase activity in the adrenal cortex of castrated or immature mice treated with testosterone. A somewhat different series of effects was found following administration of estrogens to castrated male mice (144, 145): no effect on alkaline or acid phosphatase of liver or kidney, but marked increases of both liver and kidney arginase. When histological study of the mouse kidney alkaline phosphatase was undertaken, it was found that castration caused a decrease in size of the cells of the proximal convoluted tubule but a concentration of the enzyme. Under androgen stimulation, the kidney cells became larger and the alkaline phosphatase activity progressively decreased in the tubule from the distal to the glomerular end.

Hypophysectomy increased the acid phosphatase of serum, ac-

cording to Buchwald & Hudson (36), but decreased the alkaline phosphatase of bone. Stilbestrol treatment then lowered the serum acid phosphatase, but neither this estrogen nor testosterone altered the serum or fecal calcium and phosphorus. Li, Kalman & Evans (161) found that the decreased plasma alkaline phosphatase of hypophysectomized young rats could be raised by injection of growth hormone. In agreement with previously observed antagonistic effects on bone formation and general body growth, the simultaneous injection of adrenocorticotropin (ACTH) prevented the growth hormone effect.

Arzac & Blanchet (6) reported increased endometrial alkaline phosphatase activity during the proliferative stage of the human menstrual cycle, followed by an increase in glycogen content during the progestational phase. Blood alkaline phosphatase more than doubled during the first three months of pregnancy in the human (67), rose still further at the time of delivery, and then decreased slowly to return to normal by three months post partum. Although the source of the enzyme was clearly in the maternal organism, since cord blood was lower in activity, much higher phosphatase values were encountered in the case of a pregnancy with twins. Stafford, McShan & Meyer (240) found no marked changes in concentration of acid or alkaline phosphatase activities in the rat corpus luteum during pregnancy, but a marked increase in total activity of the entire corpus since it increased so greatly in size.

Pritchard reported increased alkaline phosphatase in the decidua and fetal membranes of the rat during pregnancy (200). The enzyme was predominantly nuclear in distribution during stages of cellular proliferation and differentiation, but fully differentiated cells carrying out exchange of materials with the fetus showed considerable enzyme activity to be located in the peripheral cytoplasm. Folley & Greenbaum (81) found increased arginase and alkaline phosphatase in the mammary glands of pregnant and of lactating rats, with prompt decrease after weaning. When lactating animals were adrenalectomized, the liver and mammary gland arginases decreased (82) and were restored by DOCA (52). Covolo & West (51) have initiated a series of determinations on arginase activity in laked human red blood cells. Their normal values suggest a higher level for the female

than for the male and indicate a possible effect of some steroid hormones, but the considerable variations will require establishment of rigid controls.

Other hormonal influences.—Gordan & Elliott (104) observed that inhibition of *in vitro* glucose oxidation by brain paralleled the anesthetic effect of various steroids, except in the case of stilbestrol. However, no such correlation was obtained on succinate oxidation. The depression of glucose metabolism may be due to an action of the steroids on some dehydrogenases, inasmuch as methylene blue caused no reversal of the inhibition.

McShan, Meyer & Erway have found that the synthetic estrogens diethyl stilbestrol and benzestrol inhibit *in vitro* malic dehydrogenase of rat liver and succinoxidase of rat adrenals, brain, pituitary, corpora lutea, ovaries, kidneys, and heart (73, 180). However, stilbestrol injection for ten days did not result in any depression of succinoxidase or cytochrome oxidase activity in rat liver. This group of workers has also studied the changes in these enzymes in rat ovarian tissues during pregnancy and lactation (179, 181): steady increases in activity of the corpus luteum of pregnancy occurred during the first half of gestation and these were maintained through the second half. Lactation also involved increased succinic dehydrogenase, malic dehydrogenase, and cytochrome oxidase systems in the corpus luteum of lactation. These are important in the synthesis of progesterone, probably under the control of the placenta and anterior pituitary.

Following up observations on the increased cytochrome oxidase and succinoxidase activities (255) and increased cytochrome-*c* content (256) of various tissues from animals rendered hyperthyroid, Tissières showed that long-term treatment with dinitrophenol (DNP) would not cause comparable changes in muscle cytochrome-*c* (257). The inference is thus that the hyperthyroid changes are due to more specific effects of the endocrine than merely the increase in metabolic rate. Barker (13) has summarized much of his work showing dependence of the DNP stimulation of metabolism upon the level of thyroid gland function *in vivo*, but contradictory results from *in vitro* studies. Haas (114) noted decreased phosphate uptake as well as decreased glycogen levels in liver and muscle of animals given DNP. This could be considered as resulting from dissociation of anabolic processes involving phosphorylation and oxidative energy, as Loomis & Lipmann have interpreted

their results with DNP (164). This concept implies that the DNP acceleration of oxygen consumption results from the uncoupling of anabolic from catabolic processes.

Inasmuch as Watson & Pearce (273) encountered excess acid mucopolysaccharides, including hyaluronic acid, in the skin of two myxedema patients, they suggest that the edema "mucin" may be due to a hyaluronidase deficiency caused by the hypothyroidism, an interesting version of the early concept of Ord. Leonard, Perlman & Kurzrok showed testicular hyaluronidase to reach its maximum level of activity in the rat between weaning and sexual maturity (159).

Thyroid

Determination and distribution of hormonal iodine.—Studies continue to be made on the plasma protein-bound iodine (PI) as an index to thyroid function. Further adaptations of the Chaney distillation procedure and iodide catalysis of the arsenious acid-ceric sulfate reaction have been reported by Barker (14). Man and coworkers point out the especial value of the PI determination in evaluating thyroid function in childhood (168) and during the stress of pregnancy (196). Swenson & Curtis (248) concur in the usefulness of this objective analysis as do many other laboratories which have not published any separate formal report of their experience. However, lowered plasma protein levels yield decreased plasma PI's, as shown by Peters & Man (195).

Barker & Lipner (16), following up Dvoskin's observations of a thyroxine-like action of subcutaneously-injected elemental iodine (65,66), noted that a dose of 4 mg. iodine per kg. per day caused a marked elevation of plasma PI without causing any change in metabolism. With a dose of 16 mg. per kg. per day, the PI was considerably higher; a rise in metabolic rate was then obtained from the thyroidectomized and, to a lesser extent, from the thiouracil-treated animals. This no doubt represented the graded sensitivities of these various preparations to some metabolically active iodine compound, probably thyroxine. The tremendously elevated plasma PI values must represent primarily nonthyroxine material. It was reported (251) that thyroxine could be extracted directly from rat plasma without any previous hydrolysis, suggesting that the circulating thyroid hormone actually is free thyroxine. It would be premature to speculate on such things as the nature of the binding

which causes all the plasma thyroxine to be precipitated with the plasma proteins, and whether diiodotyrosine remains in the protein molecule after iodination or must be split out before thyroxine formation is possible.

Synthetic thyroxine with I^{131} in the 3′ and 5′ positions was found by Gross & Leblond (112) to show the same metabolic activity as nonradioactive synthetic thyroxine. When this material was injected into young rats, within two hours a large proportion was found to have entered the liver and passed to the gastrointestinal tract by way of the bile. About 50 per cent of the administered radioactivity was present in these structures plus the pancreas. Since 80 to 95 per cent of the material was excreted in the feces or urine within twenty-four hours, the stimulation of metabolism must be exerted by a relatively small proportion of injected thyroxine.

Pitt Rivers & Lerman (197) have found D(+)thyroxine to have approximately one tenth as much activity as the natural L(−) thyroxine when tested in myxedematous patients. Smith, Emmens & Parkes (230) presented a technique for assay of "thyroidal activity" of administered substances, based on survival time of mice confined to closed jars. They were able to show a good correlation between survival time and dose of thyroid substance administered, but the method obviously may lead to misinterpretation of a highly toxic drug as possessing thyroidal activity. Using this procedure, Smith found D(+)thyroxine nearly inactive, diiodothyronine one tenth as active as DL-thyroxine, and the following ineffective: thyroxamine, diiodothyroxamine, tetrachlorothyronine, tetrabromothyronine, and diiodotyrosine (229). On the other hand, Griesbach, Kennedy & Purves (110) reported that DL-thyroxine was two thirds as active as L(−)thyroxine when judged on the basis of preventing basophilic changes in the pituitary resulting from methyl thiouracil.

Thyroid and iodine metabolism.—Taurog, Chaikoff & Feller (252) suggest a mechanism in the thyroid gland for fixing iodide independent of any subsequent conversion to diiodotyrosine or thyroxine on the basis of their finding a normal rate of fixation of injected iodide twelve hours after administration of propylthiouracil, although no synthesis of thyroxine or diiodotyrosine was possible. Furthermore, the enlarged thyroids of animals kept for two weeks on propylthiouracil showed a greater than normal iodine

fixing capacity, presumably due to the increased vascularity and cell content. This fits in well with the work of VanderLaan & Bissell demonstrating good early iodide uptake, but an inability of the inhibited gland to retain the iodide in the absence of organic synthesizing power (264). Taurog & Chaikoff (250) have also reported data to bolster the Harington concept of diiodotyrosine as the first step in actual iodination. The specific activity of the diiodotyrosine iodine went up faster than that of the thyroxine iodine, reached a higher peak, and was falling while thyroxine activity increased. The mystery of why injected thyroxine will stimulate metabolism and diiodotyrosine will not still remains. Although the total iodine content of thyroids from eleven different vertebrates varied from 17 to 300 mg. per cent, the thyroxine iodine was 25 to 32 per cent of the total, indicating a fundamentally similar mechanism in the synthetic process (284).

Wolff & Chaikoff take up in more detail the earlier observation that high concentrations of inorganic iodine inhibit the *in vitro* synthesis of diiodotyrosine and thyroxine by thyroid tissue (285, 286). They have now shown that incorporation of I^{131} into organic iodine fractions by rat thyroid *in vivo* occurs only when the plasma inorganic iodine is below 20 to 35μg. per cent (calculated from radioactivity measurements), even though the gland still is able to fix iodine, as discussed above. These workers thus explain the favorable action of large doses of iodide upon human Graves' disease on the basis of this inhibitory action, in contrast to DeRobertis' concept of inhibition of an overactive proteolytic enzyme located in the colloid material (60). McClendon, Foster & Cavett (175) suggested that iodination of pituitary protein to form PI would directly inhibit the release of thyrotropin, and thus alleviate hyperthyroidism. Two points make this unlikely; thyrotropin secretion has been found to be quite low in thyrotoxicosis and widespread formation of iodinated protein might itself result in increased metabolism.

McClendon & Foster (174) showed by a delightfully direct experiment that young rats placed on a nearly iodine-free diet carefully prepared to eliminate all possible goiter "noxa" developed thyroid glands four times as large as controls on the same diet plus added iodide. Although agreeing with Greenwald (109) that all endemic goiter is not caused by an absolute iodine deficiency, Ucko (261) nevertheless objected to his conclusion that iodide

supplements have not caused a decreased incidence of goiter. Reviving the old question of calcium involvement in thyroid function, Simpson (228) reported increased iodine held in the thyroids of adult rats placed on a low calcium diet, although there was no increase in gland size. Prolonged injection of estrone or testosterone decreased the thyroid iodine in animals on a low-iodine diet (95).

General aspects of thyroid participation in energy metabolism.—Aleshin & Sarenko (3) found that acetylcholine applied *in vitro* to animal thyroids decreased their oxygen consumption, while epinephrine caused an increased metabolism, even if the gland had already been stimulated by thyrotropin. The authors consider that a basic autonomic control of thyroid metabolism established the starting level for thyrotropin stimulation. A puzzling claim of secretion of a thyroid-stimulating hormone by the spleen was advanced by Moszkowska on the basis of a lowering of hyperactive thyroid epithelium after splenectomy (187).

The effects of long-continued administration of desiccated thyroid to guinea-pigs (up to 254 days) have been reported by Layani, Aschkenasy & Mignot (154, 155). Thyroid depression was very marked. Many bony changes were indicative of withdrawal of calcium and phosphorus together with fibrosis, but no marked osteoclastic activity. Serum calcium was elevated, as was the phosphatase. The bone marrow was found markedly hyperactive, but there was no change in blood hemoglobin. Hoffmann *et al.* called attention to the importance of a source of adrenal cortical hormones for thyroxine to exert its usual stimulation of oxygen consumption (122).

Abelin & Klingler (2) have found that experimental hyperthyroidism caused a marked decrease in fat content of the body, due mostly to loss of fat from subcutaneous stores and muscle. Shipley, Chudzek & György (226) reported thyroidectomy, adrenalectomy and hypophysectomy all prevented the development of fatty livers in rats on a high-fat low-lipotropin diet. Using dogs fed a high-protein diet adequate in lipotropic agents, Entenman and coworkers (71) were able to produce fatty livers slowly after thyroidectomy alone, and much more rapidly when thyroidectomy was superimposed upon hypophysectomy. Addition of choline to the diet (70) prevented the fatty livers, but had no influence on the hyperlipemia, indicating that chemical lipotropins cannot entirely

replace endocrine lipotropic activity. The concept of the thyroid gland as a controlling agent in fat transfer had previously been advanced by Handler (117), whose work pointed to cholesterol as a key substance. However, varying experimental conditions make it impossible to decide at present whether the thyroid effect on clearing cholesterol from the liver is due to increased transport and distribution or altered synthesis and utilization of all lipid fractions.

Johnson & Baumann obtained additional evidence that the thyroid gland is involved in the hepatic transformation of carotene into vitamin A (135). Hyperthyroid or hypothyroid weanling rats depleted of vitamin A appeared equally able to store administered A, but the hyperthyroid animals stored more in the liver and the hypothyroid less when carotene was fed. This latter situation could be reversed by injection of thyroxine but not by DNP acceleration of metabolism. Although Wiese, Deuel & Mehl (279) showed good conversion in the liver of thiouracil-treated rats when very large doses of carotene were employed, two other laboratories have reported defective carotene metabolism in hypothyroidism (40, 267). This conversion might be part of the lipid mobilization influence of the thyroid just discussed, since carotene requires bile salts for its absorption, and carotene conversion to vitamin A in the liver may require esterification at some stage. Williamson found no change in plasma vitamin A level in thyroidectomized rabbits, but a high estrogen dosage did cause a decrease (281).

Successful management of two human cases of thyrotoxicosis on massive doses of vitamin A (227) calls attention to another side of the vitamin-hormone picture. Sadhu (217) concluded that vitamin A reduced thyroid size as well as activity, through depressing the secretion of thyrotropin, "competing" with thyroxine in the periphery, and combining with thyroxine to form an inactive compound. This work cannot be considered convincing because of the enormous dosages employed: 30,000 I.U. vitamin A per rat per day and 1 gm. potassium iodide per rat per day surely are larger than should be required to show a process of reasonable physiological significance. Lipsett & Winzler (162) reported increased size and histological changes in thyroids of A-deficient rats. Although these enlarged glands took up normal amounts of I^{131}, they were not capable of a normal conversion of inorganic to thyroxine iodine. These contradictory results, indicating a depression of thyroid function with both hypo- and hypervitaminosis A, can perhaps be ex-

plained by the extremely large amounts of the vitamin used in the earlier work.

Revision of present-day concepts as to thyroid control of protein metabolism would be necessitated by Persike's finding increased protein catabolism in fed thyroidectomized rats (193). On a stock diet, containing 17 per cent protein, the thyroidectomized animals' urea excretion rose in three weeks nearly to that of the ad lib fed controls, even though the latter ate nearly twice as much. When put on a pure carbohydrate diet (35 per cent glucose solution) for four days, the urinary ureas of all animals decreased, but the athyroid the least, so that theirs was 111 per cent greater than the control excretion. White & Dougherty (276) showed that thyroidectomized mice were unable to mobilize muscle nitrogen during fasting. These two sets of findings may indicate active thyroid participation both in deposition of protein in the fed animal and in mobilization during inanition, although Persike's results with the exclusively carbohydrate diet mentioned earlier do not support this concept. Persike interpreted the smaller organ weights of the hypothyroid animals on the basis of protein withdrawal (194). Some of the data of Leathem & Seeley (156) furnish indirect support for these unorthodox views. Brown & Morgan (34) found that the utilization of casein nitrogen for growth in young rats was depressed by both vitamin A and by thyroid administration, without any cumulative effect of the two conditions.

Sadhu & Brody (215, 218) endeavored to implicate the thyroid in specific dynamic action (SDA) of amino acids, but the data show principally a time-lag difference between thiouracil-treated and normal rats. The variable, occasionally high metabolic responses to glutamic acid disagree with the wealth of evidence obtained by Lusk (167). The possibility that differences in rate of transamination of amino acids may be responsible for differences in SDA was left confused by these authors (215, 219): they correlated low transamination coefficients for glutamic and aspartic acids with Lusk's finding of no SDA for these two substances, but themselves claimed a high SDA for glutamic.

Folic acid deficiency, along with generally increased vitamin requirement, in experimental hyperthyroidism has been pointed out by Martin (171), who also noted a decrease in tissue cocarboxylase and free thiamine. When large amounts of thyroid substance were included in the food of immature female rats, growth was restricted and death resulted, probably from cardiac failure

(72). Liver and yeast preparations were able to alleviate this condition, and Ershoff concluded that the requirement for some unknown nutrient was greatly increased by the extreme hyperthyroidism. Similar results were reported by Betheil, Wiebelhaus & Lardy (24), although Allardyce *et al.* found very large amounts of B vitamins would offer protection (4). Marx, Meserve & Deuel (173) showed that a high dietary cholesterol prolonged survival time and often prevented marked weight losses in rats fed toxic doses of thyroid substance.

Decreases in metabolism averaging nearly 5 per cent after only three to seven days on a low-calorie diet (124) makes it seem less surprising that Lamy and co-workers should observe many signs of severe hypothyroidism as well as diminished function of other endocrines in prison camp internees (149).

Delayed denervation atrophy and neuromuscular regeneration were obtained in thiouracil-treated rats following nerve crush injuries by Diaz-Guerrero, Thomson & Hines (62). Injection of thyroxine accelerated both atrophy and regeneration. These altered rates of cell function are probably related to the decreased mitotic activity found by Fleischmann & Breckler in the corneas of hypothyroid rats (79). Cox found less work done by sciatic nerve-gastrocnemius preparations from both hypo- and hyperthyroid animals (53) when stimulation was carried out over a long period (20 hr.).

Inhibition of the thyroid gland.—The tremendous interest aroused by the early announcements of antithyroid agents several years ago continues to release a flood of reports, especially on clinical aspects of this subject. No review of this latter field can even be attempted here, but three summarizing articles will be cited (18, 100, 176).

Various new derivatives of thiourea, especially substituted thiouracils, continue to be tested clinically, as fundamental animal research demonstrates their efficacy. Rawson, McGinty *et al.* (178, 203) have proposed a technique of evaluating thyroid-inhibiting potency of various drugs by determining their ability to interfere with thyroid collection of radioactive iodine. Stanley & Astwood (241) applied this procedure to the human and found that many compounds previously judged on their goitrogenic abilities had to be re-evaluated as functional inhibitors. In fact, the finding that thiourea itself has the same order of activity as thiouracil and propylthiouracil makes the reported success of the Yale group (56,

282) with small doses combined with iodine seem less surprising. These workers found an actual enhancement of thiourea effect by the iodine, which makes the Miller, Roblin & Astwood (184) concept of thiouracil thyroid depression by reaction of sulfhydryls with iodine seem less probable, despite its revival by Formijue (85).

Interest in explaining inhibitors on a basis of structural similarity to some biological agent has stimulated reports pointing out the relation of thiouracil to uracil (235) and stressing the importance of nucleic acids in thyroid gland function (211). This is one of the conclusions reached by Sadhu, who was able to show some effect of uracil in preventing the thiouracil-induced hypertrophy of the thyroid (216). He also claimed a similar effect from a diet containing 10 per cent tyrosine by weight, but the data are too inconsistent to warrant any conclusion. Furthermore, in view of the marked toxic effects of 1 to 2 per cent tyrosine diets shown by Schweizer (224), it is difficult to have much confidence in one containing 10 per cent.

Lawson & Rimington confirm their earlier work on ergothioneine as a thyroid-inhibiting agent (152, 153), although Astwood & Stanley deny any such action (7), either in rats, using thyroid weight and iodine content as criteria, or in humans, judging from radioiodine uptake. Latner & Mowbray (151) claim to have found low red blood cell ergothioneine levels in thyrotoxicosis, support for the hypothesis of this substance as a humoral agent for thyroid regulation. However, demonstration of ergothioneine in the circulating plasma has not yet been reported.

Barker has made many attempts to produce permanent depression of the thyroid in rats by administration of thiouracil for periods up to fifteen months (15). Although the plasma PI often remained low, the basal metabolic rate (BMR) was permanently affected in only six rats out of eighty tried. For this reason, the question is here raised concerning "thiouracil-induced" remission in thyrotoxicosis, often estimated at as high as 60 per cent of cases treated (254). An alternate conclusion is that adequate treatment may help the patients to avoid crises, and they then spontaneously recover [cf. (12, 17)]. Kuzell *et al.* (148) stated that all rats on thiouracil-containing diets for one hundred twenty days or longer showed nodular changes together with hyperplasia and Purves & Griesbach reported thyroid adenomata in 88 per cent of rats treated with thiourea for two years (201). In this laboratory, we have

maintained rats in an underdeveloped, cretinoid condition for five hundred days, without encountering any nodules until the drug was withdrawn from the diet. Histological examination then revealed some nodules of very large follicles, but no genuine adenomata.

Abelin (1) noted that methylthiouracil decreased the effect of thyroxine or of desiccated thyroid on the rat BMR and believed that the effect was exerted primarily through aiding the liver to destroy (or perhaps to excrete) thyroxine. His findings may equally well be interpreted as demonstrating a toxic effect of methylthiouracil as Borell & Holmgren claimed for liver (30). The problem of adequate thiouracil control of thyrotoxicosis in the pregnant woman without causing damage to the fetal thyroid has been considered by Rune Frisk & Josefsson (214) and by Whitelaw (278).

The increasing availability of radioiodine (I^{131} for the most part) has spurred its use both in tracer evaluation of thyroid function and in treatment by irradiation of the gland from within. The results of many studies have not yet been presented in formal publications and newer approaches to this are constantly being offered at society meetings. Keating *et al.* have been interested in evaluating thyroid uptake of radioactivity from determinations of urinary excretion of radioactivity (139). Their findings as well as those of Quimby & McCune (202) on the direct uptake by the thyroid indicate that uptake is low in hypothyroidism and elevated in thyrotoxicosis. Stanley & Astwood have proposed a method of evaluation of human thyroid function based upon the increased accumulation of I^{131} and its discharge by either thiocyanate or nonradioactive iodide (242).

Findlay & Leblond injected two rats on a low-iodine diet with about 400 μc. I^{131} per kg., and even at this dosage found some evidence of decreased thyroid function and considerable histological evidence of damage (75). The doses of I^{131} used by Gorbman (102) were quite out of this range, and destruction was severe. Evans (74) and Leblond *et al.* (157) discussed improved methods for preparing radioautographs. Two review references on various uses of I^{131} may be cited here (138, 204).

Pancreas and Carbohydrate Metabolism

Dohan & Lukens produced degeneration of pancreatic islet cells and persistent diabetes in normal and partially depancreatized cats by repeated intraperitoneal injections of glucose (63).

The continued excessive stimulation of insulin secretion apparently caused a functional failure resulting in the histological alterations. Several workers have reported techniques for estimating the total volume of pancreatic islets in small animals (115, 188, 253). Although Tejning claimed that a high fat diet caused a decreased islet volume (253), Haist & Pugh maintained that no change resulted from fasting (115). Chakrabarty (43) found low blood sugars, lowered glucose tolerances, and histological alterations in the pancreas resulting from slow starvation during recent Bengal famines. Bicknell (25) raised interesting questions of interpretation of these findings.

Arteriovenous (AV) glucose differences of peripheral tissue have been studied by Somogyi in postabsorptive and glucose-fed healthy persons (231, 232). As the arterial blood sugar level rose, the AV difference became greater, denoting a more rapid withdrawal of glucose from the blood plasma. When the arterial level fell below its starting value, there was a marked decline in extrahepatic tissue removal of glucose. Somogyi thus called attention to the important role of extrahepatic tissues, principally muscle, in the glucose utilization side of the balancing of the blood sugar level. This effect cannot be due to insulin, which is actually called onto the scene by the arterial hyperglycemia, but more likely is due to the prompt secretion of the pituitary and adrenal glands.

Considerable work on intermediary metabolism using deuterium as a tracer has been summarized by Stetten (244). The diabetic animal was carrying out fat synthesis at only 5 per cent of the normal rapid rate and responded to insulin injections with a great rise in liver fat as well as glycogen. Greeley reported that anterior pituitary and adrenal cortex do not appear active in depancreatized herbivora and believed that this type of experimental preparation showed a nearly pure interference with carbohydrate storage, as glycogen or after transformation to fat (106). Fasting caused a decreased blood sugar, loss of glycosuria, and no increase in protein breakdown. A surprisingly similar disappearance of glycosuria occurs in the fasted alloxanized rat, and Janes & Prosser have now found that high fat diets have a similar effect (134). In addition, the ketonuria was not consistently elevated.

Vandenbroeck & Férin have reported a considerable decrease in insulin requirement of a diabetic woman following development of pituitary insufficiency (263). Four of seven menopausal diabetic

patients, well stabilized on food and insulin, showed a 25 to 50 per cent decrease in insulin need with intensive estrogen therapy for three months (169). This is contrary to the exacerbation of alloxan diabetes in the force-fed rat which Ingle *et al.* brought about by various estrogens (125, 128).

Ellenberg & Pollack presented pathological and electroencephalographic evidence of cerebral damage present in two cases of diabetes mellitus associated with nonhypoglycemic reactions (69). These changes probably represent the lasting effects of previous episodes of insulin hypoglycemia shown by Olsen & Klein to result in lowered brain carbohydrates and acid-labile phosphate (191). Decreased glucose and insulin tolerances were noted by Kelley & McDonald when dogs were exposed to simulated altitudes of 18,000 and 24,000 feet (141).

Banerjee & Ghosh (10) have extended their earlier work to show that vitamin C deficiency in guinea pigs lowered the pancreatic insulin content, causing decreased glucose tolerance and decreased liver glycogen levels. Sherry & Ralli (225) found the injection of insulin caused a temporary decrease in plasma and urine vitamin C, probably because of transfer of the vitamin into the tissues, perhaps for some catalytic function. The increase in blood diphosphothiamine resulting from intravenous injection of thiamine into dogs was considerably enhanced by a previous injection of insulin (80). Since the blood inorganic P also decreased slightly, the conclusion was reached that insulin catalyzed the phosphorylation of thiamine, possibly in the liver. It is difficult to explain the observations of Vuylsteke (271), wherein the polyneuritic pigeon may react fatally to less than one tenth of the dose of insulin which a normal bird tolerates well.

Ingle, Prestrud & Nezamis found that the rise in blood amino acid level of rats over the twenty-four-hour period following evisceration could be diminished or even suppressed by the infusion of adequate amounts of glucose and insulin (131). Reid noted that insulin caused hypoglycemia and decreased the storage of liver glycogen in eighteen-hour fasted mice given alanine, lactate, or pyruvate (205). This effect indicates a more deep-seated action of insulin than the simple inhibition of deamination. An interesting extension of this work was performed by Bone & Reid, who produced a marked fall in blood amino acids by insulin hypoglycemia in cats (29). The administration of either carbohydrate or fat

prevented the blood amino acid changes, although the fat had no effect on the blood sugar.

Some renewed attention has been paid to the modification of insulin effect by previous diet. Reid (206) reported that the fall in blood sugar after insulin occurred at the same rate in fasted mice after a high protein diet or a control diet, but the former developed hypoglycemic symptoms more slowly because of the higher starting liver glycogen. On the other hand, Cunningham, Barnes & Todd (54) found that the liver glycogen level in rats previously fed a diet with 15 per cent glycine was lower, but fell less rapidly after insulin injections than in the controls, indicating increased glyconeogenesis. These same workers previously showed (258) that glycine had some specific catalytic effect on glyconeogenesis, which process required the presence of the adrenals.

Two reviews cover the relationships between various endocrines and their effects on carbohydrate metabolism (190, 280), and a third discusses the effects of pancreatectomy in man (96).

Adrenal Cortex

Carbohydrate metabolism.—Ingle, Prestrud & Nezamis (132), following up earlier work, showed that prior adrenalectomy prevented the rise in blood amino acids upon evisceration. Ingle *et al.* found that the only time administration of ACE caused a significant rise in blood sugar level in glucose-infused eviscerated rats was when insulin was also being injected (133). This makes it appear that the ACE was most active when the glucose load was the greatest, certainly not the usual condition of adrenal cortical activity. Ingle & Nezamis believed they had shown an increased utilization of infused glucose in the eviscerated-adrenalectomized preparation in comparison to the eviscerated, but with the greatest difference appearing in the noninsulin treated and an apparent reversal at higher glucose plus insulin dosages (127). "Glucose utilization" in these studies was judged solely by comparison of blood sugar levels at the termination of the perfusion period. Since there was no glycosuria in any group, the true glucose utilization is the glucose infused corrected for differences in the terminal blood sugar. These latter adjustments are not great, the maximum being 48 mg. per cent in comparison with 1056 mg. of glucose perfused per 100 gm. body weight over the twenty-four-hour period. Such calculations reveal meager differences quite different

from the marked changes produced in the metabolism of intact animals over longer periods of time.

Ingle & Prestrud (129) partially depancreatized rats accustomed to force-feeding of a constant diet and found the excretion of about half as much glucose per day as was ingested, which amount gradually decreased to zero after adrenalectomy, and the urine nitrogen fell to normal levels. Injection of ACE caused a prompt rise in glycosuria and a delayed increase in nitrogen excretion. These results support the concept that the adrenal cortical secretions exert a considerable inhibiting control over carbohydrate utilization. Brownell & Hartman noted a greater than normal ability to form and store liver glycogen during fasting in mice two to four weeks after bilateral adrenal enucleation (35).

Some discrepancies are turning up in the usually specific activities of DOCA and 11-oxysteroids. Although the greater effect of DOCA on lactation found by Cowie *et al.* (52) can be explained on the basis of increased water content (83), this same steroid was found to cause a better restoration of the depleted liver glycogen of adrenalectomized rats than 11-dehydrocorticosterone. This sort of finding reminds one of the effects of a high sodium intake on carbohydrate levels, for which only the explanation of improved well-being of the animal providing better conditions for enzyme activity can be offered [cf. Young (287)]. The beneficial effects of 1 per cent sodium chloride as drinking water for adrenalectomized rats has again been shown by Ingle & Nezamis (126), who also found the testis to have no influence on survival. Bondy & Engel report the survival time of adrenalectomized-nephrectomized rats previously on a low-potassium diet to be longer than unoperated and the uremia at death below that of the controls (28). Administration of ACE reversed these effects.

Fat metabolism.—Young (287) mentioned the possible involvement of the adrenal cortices in fat mobilization into the liver, which is supported by the evidence of Hartman, Brownell & Knouff (118). Schiffer & Wertheimer (223) showed that adrenalectomy lowered fat stores in the periphery as well as in the liver and suggested that DOCA could elevate the peripheral fat. Baker *et al.* (8) noted fatty infiltration of the livers of rats force-fed a high carbohydrate diet when ACTH was administered.

Protein metabolism.—Much interest in the adrenal cortical influence on protein metabolism has been aroused by White &

Dougherty's work with lymphoid tissue (275). These authors have recently differentiated between adrenal cortical mobilization of lymphoid tissue nitrogen and thyroid mobilization of muscle nitrogen in fasting mice (276), but also pointed out the importance of the adrenal for thyroid activity. Andreasen *et al.* (5) found no lasting effect on any blood protein fraction of extirpation of about 90 per cent of the lymphoid structures in the rat. Stoerk, John & Eisen (245) claim that the rate of serum protein turnover is not influenced by adrenalectomy or by administration of ACE to adrenalectomized rats, although Lewis & McCullagh (160) reported lowered plasma albumin and γ-globulin in Cushing's syndrome, shifted toward normal by effective x-ray or testosterone therapy. Involvement of the adrenal cortex in liver cell multiplication as well as in protein synthesis is apparent from the marked depression of adrenalectomy on regeneration after partial hepatectomy (23).

General metabolic functions.—In man, DOCA at first produced the expected retention of sodium and water, but in the second week of hormone dosage, the subject increased his water intake and produced a diuresis plus a negative sodium and potassium balance (288). Zierler & Lilienthal attribute this to inhibition of tubular reabsorption since there was no effect on glomerular filtration rate. When the DOCA was withdrawn, the typical pattern of adrenocortical hypofunction appeared, subsiding in ten days. Moehlig has made the final report on a case of Addison's disease treated for nine years, in whom necropsy showed a complete absence of adrenal glands (185). Both anterior pituitary and thyroid showed considerable fibrosis, possibly as a result of exhaustion.

Following reports of improved muscle work performance, glycogenesis as well as sodium retention in experimental animals produced by 11-dehydrocorticosterone acetate (an 11-oxycorticosteroid), trials were made on a normal woman (123) and on one with Addison's disease (236). Although there was some retention of salt and water, this was less marked than with DOCA, and there was almost no effect on carbohydrate metabolism or gluconeogenesis from protein in either subject.

Using the Selye-Schenker cold survival test in the assay of cortical hormone content, Vogt obtained ten times as much hormone per minute in the venous blood from one adrenal as

could be found in the gland itself (268). Thus, the hormones appear to be synthesized and released as needed, rather than stored; the decreased cholesterol content of the adrenal cortex found by Sayers *et al.* (221) probably was a precursor, not the actual endocrine material. Variations in blood pressure and blood flow had no effect on cortical secretion, but splanchnic stimulation, probably through epinephrine stimulation of ACTH, caused a considerable increase. Perfused adrenals showed less secretion, but an immediate and prolonged rise in response to ACTH. Vogt (270) has also found no basis for the belief based on the earlier claim of Lowenstein & Zwemer (165) that ascorbic acid actually was combined with corticosteroids. There still is no direct evidence as to the significance of the decrease in adrenal cortical ascorbic acid content following stimulation resulting in active secretion by the cortex (220); the ascorbate may be required in metabolic processes, or a fragment from it may be combined with a cholesterol derivative to form the active secretion. In extension of this work, Miller & Everett have reported increased cholesterol and ascorbic acid contents of corpora lutea after luteinizing hormone injection into pregnant rats (183).

A severe dietary deficiency of thiamine in weanling rats, like that of pantothenic acid, caused exhaustion effects on the adrenal cortical zona fasciculata (58). Depletion of cortical lipids occurs in response to low temperatures, high temperatures, and blood loss (269). An early depletion stage was followed by a later accumulation if the stimulus was continued long enough. Such diphasic changes took place following ACTH injection, pentobarbital anesthesia, severe thermal injury, or treatment with vesicants and could be followed chemically by the reducing power of the steroid side-chains or by cholesterol ester and ascorbic acid determinations (121, 166).

Forbes *et al.* have shown an early rise, then a fall, in urinary 17-ketosteroids of patients subjected to medical or surgical injury (84). Debilitated individuals have a subnormal excretion at all times, indicating part of their lack of resistance is probably due to poor response of the adrenals to stress. Landau and co-workers found a marked decrease in 17-ketosteroid excretion during fasting in human subjects (150), but D'Angelo, Gordon & Charipper considered their data in the fasting guinea pig to indicate a stim-

ulation of the adrenal cortex via pituitary ACTH (55). Addition of another quantitative steroid determination, that of 11-oxycorticosteroids ("glycogenic"), to the 17-ketosteroid and sodium retention values now being obtained under various clinical conditions promises to throw further light on adrenal cortical function (249, 265). Such findings as a low 11-oxycorticosteroid and 17-ketosteroid excretion in hypothyroidism and normal values in diabetes mellitus have important theoretical implications (19, 249, 265).

Pituitary control of adrenal cortex.—Reiss discussed some aspects of the anterior pituitary-adrenal cortical relationship (209), pointing out that the pituitary control is not absolute, since hypophysectomized animals seldom develop adrenal insufficiency. Cooke, Graetzer & Reiss (47) presented their modification of the Sayers' assay of ACTH (222), using decreased adrenal ascorbic acid content, as well as methods for concentration of ACTH in urine and plasma. Much evidence indicates the importance of epinephrine stimulation of ACTH release in the response of the adrenal cortex to stress (163, 221).

Forsham *et al.* (86) found several days' injections of ACTH into human subjects enhanced all known functions of the adrenal cortical tissue: androgenic, glycogenic, and sodium retention. No effects were shown in Addison's disease. Mason *et al.* (172) obtained increased steroid excretion under similar experimental conditions, but much less definite metabolic effects. When ACTH was injected into rats on constant dietary intake (high fat, high carbohydrate, or high protein), some of the animals on the high carbohydrate diet excreted sugar, all animals excreted more urinary nitrogen and potassium, but none showed the expected sodium retention (130). Such results with purified ACTH emphasize the differences in the pituitary control of the several adrenal cortical functions in different species. Conn, Louis & Wheeler reported glycosuria and increased urinary nitrogen in humans resulting from ACTH injections (46). The consistent increase in uric acid excretion observed in these subjects, in conjunction with Griffiths' report of temporary diabetes produced in rabbits by uric acid injection (111), raises again the possible involvement of alloxan in diabetes mellitus.

Bennett *et al.* obtained increased ketogenesis in fasted rats from both purified growth hormone (GH) and ACTH (20). The latter

required the presence of the adrenals, but the GH had a direct peripheral effect. Deane & Greep showed cytologically that the level of thyroid activity affected the zona fasciculata through pituitary mediation (57). Although there was no effect of level of protein intake upon the basal activity of the adrenal glands, Moya and co-workers found a protein-rich regime to augment the ACTH response to stress (189).

Adrenal Medulla

Leindorfer, Arana & Hack found that intracisternal injection of epinephrine caused a marked increase in blood sugar without effecting blood pressure or the electroencephalogram (EEG) (158). Various central and peripheral nerve lesions, adrenalectomy, and ligation of the common carotids brought about no alteration in the epinephrine effect. Further evidence of the participation of epinephrine in analgesia has been furnished by Friend & Harris (94), who showed bilateral adrenalectomy decreased, but did not abolish, morphine analgesia. Because of differences in kidney function response to exercise and to exogenous epinephrine Barclay, Cooke & Kenney concluded that exercise did not usually involve release of epinephrine (11).

Surtshin, Rodbard & Katz (246) noted the accumulation of pressor substances during acute severe hypoxia, which became effective when oxygen was readmitted. The same sequence of events followed injection of epinephrine during the hypoxemic phase. The authors concluded that either the heart and blood vessels were themselves unresponsive during oxygen-lack, or that oxidation products of epinephrine are the really active substances. The latter possibility fits in well with the concept of Kisch that adrenochrome, not epinephrine, is the metabolically active material (143). Halse & Marquardt (116) reported changes in tissue glycogen and blood sugar levels from oral adrenochrome which, together with Meyerhof & Randall's findings of adrenochrome inhibition of glycolysis (182), are difficult to fit into epinephrine activity. Franck, Grandpierre and co-workers claimed diminished epinephrine effectiveness after oxygen breathing and slight hemorrhage in chloralosed dogs (87, 105). According to Oster & Smith (192), injection of epinephrine had very little effect on time of resistance to anoxia of cats, or on the anoxic hyperglycemia.

Bülbring, Burn & de Elío (37) found the epinephrine secretion by the perfused dog adrenal gland to be increased by anoxemia, deficient circulation, potassium cyanide injection, and splanchnic stimulation. Reid reported the isolation of a substance from serum and from the buffy coat of horse red blood cells which directly caused secretion by the medullary cells of the cat adrenal (207). Gurin & Delluva showed the synthesis *in vivo* of epinephrine from phenylalanine labeled with C^{14} in the carboxyl and α-carbons (113).

Anterior Pituitary

White, Heinbecker & Rolf (277) reported that APE increased the oxygen consumption and cardiac output in the normal dog to an extent comparable to the previously determined increase in renal blood flow. Following thyroidectomy, APE caused a definite, but lowered, effect on the decreased oxygen consumption and cardiac output, and the authors concluded that the pituitary controlled metabolism through some other path than the thyroid. However, thyroidectomy following hypophysectomy produced a still further decrease in BMR and cardiac output.

Confirming Best & Campbell's early observations on a fat-mobilizing principle of the anterior pituitary, Weil & Stetten suggested the name "adipokinin" for this material (274). The presence of adipokinetic activity was shown in the urine of twenty-four and forty-eight-hour fasted rabbits, but not of normal or alloxan-diabetic. Although Bennett *et al.* found no increased ketonemia from lactogenic hormone (20), Reiss claimed a reduction in peripheral fat deposits, an effect which was enhanced by thyroxine (208).

Globus, Goldfarb & Silver have reviewed some clinical aspects of hypophysio-hypothalamic interrelations (99). Lesions placed in the lateral hypothalamus or in the fibers of the fornix causing hyperphagia and possibly increased absorption of carbohydrate also result in marked cellular degeneration in the anterior pituitary (234). Keller & Breckenridge removed varying amounts of pituitary stalk in dogs and concluded, since the effects were less marked than after complete hypophysectomy, that carbohydrate metabolism was not controlled through hypothalamic-pituitary paths (140). It is obvious that such observations have considerable bearing on the functional importance of the recently-discovered

vascular bed linking the neuro- and adenohypophysis (108). Giroud & Desclaux discussed histological localization of secretions of the anterior pituitary hormones (98).

Growth

Some consideration should certainly be given to the reawakened interest in control of the important anabolic process of growth. In an abstract without data, Roy touched upon the influence of several endocrines upon growth of the rat (213). APE had the most profound effect, but could be reinforced by thyroxine. ACE had little added effect, even upon adrenalectomized animals, and others have shown ACTH to inhibit growth [Ingle *et al.* (130)]. Bennett & Li showed purified pituitary growth hormone (GH) produced nitrogen retention in alloxan-diabetic rats, although it often enhanced the glycosuria (21). ACTH consistently increased both nitrogen and glucose excretion. Injection of insulin did not materially affect the results. Gordan *et al.* found that increasing the dietary protein to 24 per cent gave greater nitrogen retention and body weight increase on a standard dose of GH (103). Fishman, Wilhelmi & Russell have presented a method for the preparation of a crystalline fraction of beef APE exhibiting high growth hormone activity (78).

It was found by Canzanelli, Guild & Rapport (42) that slices of liver from hyperthyroid rats formed only about 60 per cent of the control amount of α-amino nitrogen when incubated with pyruvate and ammonia. Thyroidectomy also depressed the synthesis, but not to such a significant extent. Friedberg & Greenberg carried out an extensive survey of hormonal influences on blood and tissue free amino acid levels (90). In general, thyroxine, ACE, and protein starvation caused increases, whereas insulin, estrogen, hypophysectomy, and hypothyroidism caused decreases. A series of observations pertinent to this discussion was carried out by Deitrick, Whedon & Shorr on the effects of plaster cast immobilization on various metabolic functions of four normal, healthy, young men (59). Although the dietary intake was carefully controlled, decreased blood volume and negative nitrogen, sodium, potassium, calcium, phosphate, and sulfur balances were caused by immobilization.

Several groups of workers have shown incorporation of isotope-

labeled amino acids into tissue proteins and peptides under various *in vivo* and *in vitro* conditions (26, 88, 93, 107, 283). Normal or hypophysectomized rats injected with GH for three days showed a 30 and 70 per cent greater uptake, respectively, of S^{35}-labeled methionine in muscle protein than uninjected controls (91). Friedberg & Greenberg mentioned that the opposite effect was seen in the liver, i.e., reduction in amino acid uptake—and concluded that the growth hormone may not promote protein synthesis in all tissues. Frantz and co-workers demonstrated that DNP inhibited the incorporation of tagged alanine into liver slice proteins (89), suggesting the involvement of phosphate bond energy in protein synthesis [Loomis & Lipmann (164)]. When the effect of growth was studied, Friedberg, Schulman & Greenberg (92) reported the highest rate of tagged glycine incorporation was into the proteins of whole embryo, then into fetal liver protein. After birth, the rate of protein synthesis fell off rapidly, reaching a steady turnover in maturity. These results indicate growth to be due to very rapid synthesis, not merely inhibition of breakdown.

Reinterpretation of β-glucuronidase activity in terms of active tissue proliferation instead of sex hormone activity has been offered by Kerr, Levvy & Campbell (142). These workers showed increased β-glucuronidase values for regenerating liver, as well as liver and kidney from baby mice. They considered Fishman & Anlyan's observations (77) of high tumor β-glucuronidase activity as due to the increased growth rate. Presumably, the maternal serum increases found after the first ten weeks of human pregnancy (177) could also be so interpreted, but the still greater changes found in eclampsia, where growth is certainly no faster, do not seem related. Fisher & Glick (76) have noted concentration of alkaline phosphatase activity in proliferating tissue.

Parathyroids and Calcium Metabolism

Tweedy, Chilcote & Patras (260) have shown that thyroparathyroidectomy in the rat caused an early diminution in urinary and fecal excretion of administered phosphate tagged with P^{32}. This could be reversed within one hour by the injection of parathyroid extract; after bilateral nephrectomy, injection of this material had no effect on the distribution, retention, or excretion of P^{32}. These results strongly support the concept that the parathyroid glands have their primary influence on phosphate metabolism

through a direct action on the kidneys, but cannot, in themselves, disprove the view that the parathyroids may also influence osteoclastic activity in the bones.

The parathyroids of the duck showed seasonal variations, cellular size increasing in the spring and decreasing in the fall (22). These changes were so similar to those occurring in the gonads that it seemed probable to Benoit & Clavert that they were due to the effects of light on the animal's pituitary which, in turn, altered the parathyroids. However, there were no significant blood calcium changes.

Walsh & Howard have described unusual conjunctival and corneal lesions which seem referable to hypercalcemia (272). The involvement of calcium metabolism in thyrotoxicosis and in diseases of carbohydrate metabolism has been pointed out by Moehlig & Abbott (186). Stephenson & McNamara have reviewed the embryology, anatomy, and histology of the parathyroids and discussed clinical aspects of hyperparathyroidism (243).

Dynamic Aspects of Biochemistry

It would not be fitting to terminate this review without at least a brief mention of Baldwin's stimulating treatise published under the above title (9).

LITERATURE CITED

1. ABELIN, I., *Arch. intern. pharmacodynamie*, **75**, 187–209 (1947)
2. ABELIN, I., AND KLINGLER, K., *Helv. Physiol. et Pharmacol. Acta.*, **6**, 1–20 (1948)
3. ALESHIN, B. V., AND SARENKO, P. F., *Am. Rev. Soviet Med.*, **4**, 269–70 (1947)
4. ALLARDYCE, J., GORANSON, E. S., AND SINGER, E., *Trans. Roy. Soc. Can.* [V]**41**, 35–48 (1947)
5. ANDREASEN, E., BING, J., GOTTLIEB, O., AND HARBOE, N., *Acta Physiol. Scand.*, **15**, 254–63 (1948)
6. ARZAC, J. P., AND BLANCHET, E., *J. Clin. Endocrinol.*, **8**, 315–24 (1948)
7. ASTWOOD, E. B., AND STANLEY, M. M., *Lancet*, **II**, 905–6 (1947)
8. BAKER, B. L., INGLE, D. J., LI, C. H., AND EVANS, H. M., *Am. J. Anat.*, **82**, 75–103 (1948)
9. BALDWIN, E., *Dynamic Aspects of Biochemistry*, 457 pp. (The Macmillan Co., New York, 1947)
10. BANERJEE, S., AND GHOSH, N. C., *J. Biol. Chem.*, **168**, 207–11 (1947)
11. BARCLAY, J. A., COOKE, W. T., AND KENNEY, R. A., *Am. J. Physiol.*, **151**, 621–25 (1947)
12. BARFRED, A., *Am. J. Med. Sci.*, **214**, 349–62 (1947)
13. BARKER, S. B., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 292 (1947)
14. BARKER, S. B., *J. Biol. Chem.*, **173**, 715–24 (1948)
15. BARKER, S. B. (Unpublished data)
16. BARKER, S. B., AND LIPNER, H. J., *J. Clin. Endocrinol.*, **8**, 596 (1948)
17. BARTELS, E. C., *Am. J. Med.*, **2**, 150–55 (1947)
18. BARTELS, E. C., *Western J. Surg. Obstet. Gynecol.*, **56**, 226–35 (1948)
19. BENDA, C. E., AND BIXBY, E. M., *J. Clin. Endocrinol.*, **7**, 503–18 (1947)
20. BENNETT, L. L., KREISS, R. E., LI, C. H., AND EVANS, H. M., *Am. J. Physiol.*, **152**, 210–15 (1948)
21. BENNETT, L. L., AND LI, C. H., *Am. J. Physiol.*, **150**,, 400–4 (1947)
22. BENOIT, J., AND CLAVERT, J., *Acta Anat.*, **4**, 49–53 (1947)
23. BERMAN, D., SYLVESTER, M., HAY, E. C., AND SELYE, H., *Endocrinology*, **41**, 258–62 (1947)
24. BETHEIL, J. L., WIEBELHAUS, V. D., AND LARDY, H. A., *J. Nutrition*, **34**, 431–41 (1947)
25. BICKNELL, F., *Lancet*, **I**, 728 (1948)
26. BLOCH, K., AND ANKER, H. S., *J. Biol. Chem.*, **169**, 765–66 (1947)
27. BLOCH, K., AND KRAMER, W., *J. Biol. Chem.*, **173**, 811–12 (1948)
28. BONDY, P. K., AND ENGEL, F., *Proc. Soc. Exptl. Biol. Med.*, **66**, 104–7 (1947)
29. BONE, A. H., AND REID, C., *J. Physiol. (London)*, **107**, 5P (1948)
30. BORELL, U., AND HOLMGREN, H., *Endocrinology*, **42**, 427–35 (1948)
31. BROH-KAHN, R. H., AND MIRSKY, I. A., *Science*, **106**, 148–49 (1947)
32. BROH-KAHN, R. H., AND MIRSKY, I. A., *Arch. Biochem.*, **16**, 87–107 (1948)
33. BROH-KAHN, R. H., MIRSKY, I. A., PERISUTTI, G., AND BRAND, J., *Arch. Biochem.*, **17**, 367–78 (1948)
34. BROWN, E. F., AND MORGAN, A. F., *J. Nutrition*, **35**, 439–52 (1948)
35. BROWNELL, K. A., AND HARTMAN, F. A., *Endocrinology*, **42**, 232–35 (1948)

36. BUCHWALD, K. W., AND HUDSON, L., *Endocrinology*, **41**, 111–18 (1947)
37. BÜLBRING, E., BURN, J. H., AND DE ELÍO, F. J., *J. Physiol. (London)*, **107**, 222–32 (1948)
38. BUNTING, H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 370–72 (1948)
39. BURGEN, A. S. V., AND LORCH, J. I., *Biochem. J.*, **41**, 223–26 (1947)
40. CANADELL, J. M., AND VALDECASAS, F. G., *Experientia*, **3**, 35–36 (1947); *Chem. Abstracts*, **41**, 4549 (1947)
41. CANTOR, M. M., TUBA, J., AND CAPSEY, P. A., *Science*, **105**, 476–77 (1947)
42. CANZANELLI, A., GUILD, R., AND RAPPORT, D., *Endocrinology*, **41**, 108–9 (1947)
43. CHAKRABARTY, M. L., *Lancet*, **I**, 596–97 (1948)
44. COHEN, J. A., *Nature*, **160**, 871–72 (1947)
45. COLOWICK, S. P., CORI, G. T., AND SLEIN, M. W., *J. Biol. Chem.*, **168**, 583–96, (1947)
46. CONN, J. W., LOUIS, L. H., AND WHEELER, C. E., *J. Lab. Clin. Med.*, **33**, 651–61 (1948)
47. COOKE, D. S., GRAETZER, E., AND REISS, M., *J. Endocrinol.*, **5**, lxxxix (1948)
48. CORI, C. F., *Wash. Univ. Med. Alumni Quart.*, **10**, 117–32 (1947)
49. CORKILL, A. B., AND NELSON, J. F., *Med. J. Australia*, **I**,, 172–74 (1947)
50. CORKILL, A. B., AND NELSON, J. F., *Australian J. Exptl. Biol. Med. Sci.*, **25**, 347–49 (1947)
51. COVOLO, G. C., AND WEST, R., *J. Clin. Endocrinol.*, **7**, 325–30 (1947)
52. COWIE, A. T., FOLLEY, S. J., FRENCH, T. H., AND GREENBAUM, A. L., *J. Endocrinol.*, **5**, xxxiii–xxxiv (1947)
53. COX, L. W., *Quart. J. Exptl. Physiol.*, **34**, 115–22 (1948)
54. CUNNINGHAM, L., BARNES, J. M., AND TODD, W. R., *Arch. Biochem.*, **16**, 403–7, (1948)
55. D'ANGELO, S. A., GORDON, A. S., AND CHARIPPER, H. A., *Endocrinology*, **42**, 399–411 (1948)
56. DANOWSKI, T. S., MAN, E. B., ELKINTON, J. R., PETERS, J. P., AND WI.'KLER, A. W., *Am. J. Med. Sci.*, **215**, 123–29 (1948)
57. DEANE, H. W., AND GREEP, R. O., *Endocrinology*, **41**, 243–57 (1947)
58. DEANE, H. W., AND SHAW, J. H., *J. Nutrition*, **34**, 1–19 (1947)
59. DEITRICK, J. E., WHEDON, G. D., AND SHORR, E., *Am. J. Med.*, **4**, 3–36 (1948)
60. DEROBERTIS, E., *Western J. Surg. Obstet. Gynecol.*, **56**, 253–67 (1948)
61. DEWAELE, H., *Arch. intern. physiol.*, **55**, 209–35 (1948)
62. DIAZ-GUERRERO, R., THOMSON, J. D., AND HINES, H. M., *Am. J. Physiol.*, **151**, 91–95 (1945)
63. DOHAN, F. C., AND LUKENS, F. D. W., *Endocrinology*, **42**, 244–62 (1948)
64. DRABKIN, D. L., AND MARSH, J. B., *J. Biol. Chem.*, **171**, 455–62 (1947)
65. DVOSKIN, S., *Endocrinology*, **40**, 334–52 (1947)
66. DVOSKIN, S., *Endocrinology*, **41**, 331–33 (1947)
67. DUMONT, M., AND BERGER, R., *Lyon méd.*, **179**, 69–74 (1948)
68. ELFTMAN, H., *Endocrinology*, **41**, 85–91 (1947)
69. ELLENBERG, M., AND POLLACK, H., *Am. J. Med. Sci.*, **214**, 503–6 (1947)
70. ENTENMAN, C., CHAIKOFF, I. L., GILLMAN, T., AND REICHERT, F. L., *Endocrinology*, **42**, 215–22 (1948)

71. ENTENMAN, E., CHAIKOFF, I. L., AND REICHERT, F. L., *Endocrinology*, **42**, 210–14 (1948)
72. ERSHOFF, B. H., *Arch. Biochem.*, **15**, 365–78 (1947)
73. ERWAY, W. F., MEYER, R. K., AND MCSHAN, W. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 291–95 (1947)
74. EVANS, T. C., *Radiology*, **49**, 206–13 (1947)
75. FINDLAY, D., AND LEBLOND, C. P., *Am. J. Roentgenol., Radium Therapy* **59**, 387–95 (1948)
76. FISHER, I., AND GLICK, D., *Proc. Soc. Exptl. Biol. Med.*, **66**, 14–18 (1947)
77. FISHMAN, W. H., AND ANLYAN, A. J., *J. Biol. Chem.*, **169**, 449–50 (1947)
78. FISHMAN, J. B., WILHELMI, A. E., AND RUSSELL, J. A., *Science*, **106**, 402 (1947)
79. FLEISCHMANN, W., AND BRECKLER, I. A., *Endocrinology*, **41**, 266–68 (1947)
80. FOÀ, P. P., SMITH, J. A., AND WEINSTEIN, H. R., *Arch. Biochem.*, **13**, 449–59 (1947)
81. FOLLEY, S. J., AND GREENBAUM, A. L., *Biochem. J.*, **41**, 261–69 (1947)
82. FOLLEY, S. J., AND GREENBAUM, A. L., *Nature*, **160**, 364 (1947)
83. FOLLEY, S. J., AND GREENBAUM, A. L., *J. Endocrinol.*, **5**, 236–42 (1948)
84. FORBES, A. P., DONALDSON, E. C., REIFENSTEIN, E. C., JR., AND ALBRIGHT, F., *J. Clin. Endocrinol.*, **7**, 264–88 (1947)
85. FORMIJUE, P., *Acta Med. Scand.*, **130**, 107–15 (1948)
86. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G., AND HILLS, A. G., *J. Clin. Endocrinol.*, **8**, 15–66 (1948)
87. FRANCK, C., GRANDPIERRE, R., LEMAIRE, R., AND AUSCHER, C., *Compt. rend. soc. biol.*, **142**, 372–76 (1948)
88. FRANTZ, I. D., JR., LOFTFIELD, R. B., AND MILLER, W. W., *Science*, **106**, 544–45 (1947)
89. FRANTZ, I. D., JR., ZAMECNIK, P. C., REESE, J. W., AND STEPHENSON, M. L., *J. Biol. Chem.*, **174**, 773–74 (1948)
90. FRIEDBERG, F., AND GREENBERG, D. M., *J. Biol. Chem.*, **168**, 405–9 (1947)
91. FRIEDBERG, F., AND GREENBERG, D. M., *Arch. Biochem.*, **17**, 193–95 (1948)
92. FRIEDBERG, F., SCHULMAN, M. P., AND GREENBERG, D. M., *J. Biol. Chem.*, **173**, 437–38 (1948)
93. FRIEDBERG, F., WINNICK, T., AND GREENBERG, D. M., *J. Biol. Chem.*, **169**, 763–64 (1947)
94. FRIEND, F. J., AND HARRIS, S. C., *J. Pharmacol. Exptl. Therap.*, **93**, 161–67 (1948)
95. GASSNER, F. X., BARRETT, H. W., AND GUSTAVSON, R. G., *Western J. Surg. Obstet. Gynecol.*, **56**, 346–59 (1948)
96. GASTON, E. A., *New Engl. J. Med.*, **238**, 345–54 (1948)
97. GEMMILL, C. L., *Bull. Johns Hopkins Hosp.*, **68**, 329–36 (1941)
98. GIROUD, A., AND DESCLAUX, P., *Ann. endocrinol. (Paris)*, **8**, 276–80 (1947)
99. GLOBUS, J. H., GOLDFARB, A. I., AND SILVER, S., *J. Mt. Sinai Hosp. N. Y.*, **14**, 308–46 (1947)
100. GOODWIN, J. F., *Post Graduate Med. J.*, **24**, 206–13 (1948)
101. GORANSON, E. S., HAMILTON, J. E., AND HAIST, R. E., *J. Biol. Chem.*, **174**, 1–9 (1948)
102. GORBMAN, A., *Proc. Soc. Exptl. Biol. Med.*, **66**, 212–13 (1947)

103. GORDAN, G. S., BENNETT, L. L., LI, C. H., AND EVANS, H. M., *Endocrinology*, **42**, 153–60 (1948)
104. GORDAN, G. S., AND ELLIOTT, H. W., *Endocrinology*, **41**, 517–18 (1947)
105. GRANDPIERRE, R., FRANCK, C., AND LEMAIRE, R., *Compt. rend. soc. biol.*, **142**, 378–80 (1948)
106. GREELEY, P. O., *Am. J. Physiol.*, **150**, 46–51 (1947)
107. GREENBERG, D. M., AND WINNICK, T., *J. Biol. Chem.*, **173**, 199–204 (1948)
108. GREENE, J. D., AND HARRIS, G. W., *J. Endocrinol.*, **5**, 136–46 (1947)
109. GREENWALD, I., *J. Clin. Endocrinol.*, **6**, 708–41 (1946)
110. GRIESBACH, W. E., KENNEDY, T. H., AND PURVES, H. D., *Nature*, **160**, 192–93 (1947)
111. GRIFFITHS, M., *J. Biol. Chem.*, **172**, 853–54 (1948)
112. GROSS, J., AND LEBLOND, C. P., *J. Biol. Chem.*, **171**, 309–20 (1947)
113. GURIN, S., AND DELLUVA, M., *J. Biol. Chem.*, **170**, 545–50 (1947)
114. HAAS, H. T. A., *Arch. exptl. Path. Pharmakol.*, **204**, 110–29 (1947)
115. HAIST, R. E., AND PUGH, E. J., *Am. J. Physiol.*, **152**, 36–41 (1948)
116. HALSE, T., AND MARQUARDT, P., *Enzymologia*, **12**, 246–50 (1948)
117. HANDLER, P., *J. Biol. Chem.*, **173**, 295–303 (1948)
118. HARTMAN, F. A., BROWNELL, K. A., AND KNOUFF, R. A., *Endocrinology*, **41**, 213–19 (1947)
119. HEARD, R. D. H., LOZINSKI, E., STEWART, L., AND STEWART, R. D., *J. Biol. Chem.*, **172**, 857–58 (1948)
120. HECTOR, O., LEVINE, R., AND SOSKIN, S., *Proc. Soc. Exptl. Biol. Med.*, **46**, 390–93 (1941)
121. HEMPHILL, R. E., AND REISS, M., *Endocrinology*, **41**, 17–20 (1947)
122. HOFFMANN, F., HOFFMANN, E. J., AND TALESNIK, J., *J. Physiol. (London)*, **107**, 251–64 (1948)
123. HOMBURGER, F., ABELS, J. C., AND YOUNG, N. F., *Am. J. Med.*, **4**, 163–74 (1948)
124. HUSBY, J., *Acta Med. Scand.*, **130**, 20–25 (1948)
125. INGLE, D. J., AND HOGG, J. A., *Proc. Soc. Exptl. Biol. Med.*, **66**, 244–47 (1947)
126. INGLE, D. J., AND NEZAMIS, J. E., *Am. J. Med. Sci.*, **214**, 286–87 (1947)
127. INGLE, D. J., AND NEZAMIS, J. E., *Am. J. Physiol.*, **152**, 598–602 (1948)
128. INGLE, D. J., NEZAMIS, J. E., AND PRESTRUD, M. C., *Endocrinology*, **41**, 207–12 (1947)
129. INGLE, D. J., AND PRESTRUD, M. C., *Am. J. Physiol.*, **152**, 603–8 (1947)
130. INGLE, D. J., PRESTRUD, M. C., LI, C. H., AND EVANS, H. M., *Endocrinology*, **41**, 170–76 (1947)
131. INGLE, D. J., PRESTRUD, M. C., AND NEZAMIS, J. E., *Am. J. Physiol.*, **150**, 682–85 (1947)
132. INGLE, D. J., PRESTRUD, M. C., AND NEZAMIS, J. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 321–22 (1948)
133. INGLE, D. J., PRESTRUD, M. C., NEZAMIS, J. E., AND KUIZENGA, M. H., *Am. J. Physiol.*, **150**, 423–27 (1947)
134. JANES, R. G., AND PROSSER, M., *Am. J. Physiol.*, **151**, 581–87 (1947)
135. JOHNSON, R. M., AND BAUMANN, C. A., *J. Biol. Chem.*, **171**, 513–21 (1947)
136. JOSLIN, E. P., KRALL, L. P., BAILEY, C. C., ROOT, H. F., WHITE, P., AND MARBLE, A., *New Engl. J. Med.*, **238**, 401–7 (1948)

137. KALCKAR, H. M., *Nature*, **160**, 143–47 (1947)
138. KEATING, F. R., JR., *Postgraduate Med.*, **3**, 410–22 (1948)
139. KEATING, F. R., JR., POWER, M. H., BERKSON, J., AND HAINES, S. F., *J. Clin. Invest.*, **26**, 1138–51 (1947)
140. KELLER, A. D., AND BRECKENRIDGE, C. G., *Am. J. Physiol.*, **150**, 222–28 (1947)
141. KELLEY, V. C., AND MCDONALD, R. K., *Am. J. Physiol.*, **152**, 250–56 (1948)
142. KERR, L. M. H., LEVVY, G. A., AND CAMPBELL, J. G., *Nature*, **160**, 572 (1947)
143. KISCH, B., *Exptl. Med. and Surg.*, **5**, 166–81 (1947)
144. KOCHAKIAN, C. D., *Am. J. Physiol.*, **151**, 126–29 (1947)
145. KOCHAKIAN, C. D., *Am. J. Physiol.*, **152**, 257–62 (1948)
146. KOCHAKIAN, C. D., AND VAIL, V. N., *J. Biol. Chem.*, **169**, 1–6 (1947)
147. KRAHL, M. E., AND CORI, C. F., *J. Biol. Chem.*, **170**, 607–18 (1947)
148. KUZELL, W., TRIPI, H., GARDNER, G., AND LAQUEUR, G., *Science*, **107**, 374–75 (1948)
149. LAMY, M., LAMOTTE, M., AND LAMOTTE-BARRILLOU, S., *Ann. endocrinol. (Paris)*, **8**, 437–47 (1947)
150. LANDAU, R. L., KNOWLTON, K., ANDERSON, D., BRANDT, M. B., AND KENYON, A. T., *J. Clin. Endocrinol.*, **8**, 133–45 (1948)
151. LATNER, A. L., AND MOWBRAY, R., *Biochem. J.*, **42**, xxxv (1948)
152. LAWSON, A., AND RIMINGTON, C., *Lancet*, **II**, 906–7 (1947)
153. LAWSON, A., AND RIMINGTON, C., *J. Endocrinol.*, **5**, lxiii (1947)
154. LAYANI, F., ASCHKENASY, A., AND MIGNOT, J., *Ann. endocrinol. (Paris)*, **8**, 205–25 (1947)
155. LAYANI, F., MIGNOT, J., CHAMPEAU, M., AND ASCHKENASY, A., *Ann. endocrinol. (Paris)*, **8**, 307–17 (1947)
156. LEATHEM, J. H., AND SEELEY, R. D., *Endocrinology*, **42**, 150–52 (1948)
157. LEBLOND, C. P., PERCIVAL, W. L., AND GROSS, J., *Proc. Soc. Exptl. Biol. Med.*, **67**, 74–76 (1948)
158. LEINDORFER, A., ARANA, R., AND HACK, M. H., *Am. J. Physiol.*, **150**, 588–95 (1947)
159. LEONARD, S. L., PERLMAN, P. L., AND KURZROK, R., *Endocrinology*, **42**, 176–80 (1948)
160. LEWIS, L. A., AND MCCULLAGH, E. P., *J. Clin. Endocrinol.*, **7**, 559–65 (1947)
161. LI, C. H., KALMAN, C., AND EVANS, H. M., *J. Biol. Chem.*, **169**, 625–29 (1947)
162. LIPSETT, M. B., AND WINZLER, R. J., *Endocrinology*, **41**, 494–500 (1947)
163. LONG, C. N. H., *Federation Proc.*, **6**, 461–71 (1947)
164. LOOMIS, W. F., AND LIPMANN, F., *J. Biol. Chem.*, **173**, 807 (1948)
165. LOWENSTEIN, B. E., AND ZWEMER, R. L., *Endocrinology*, **39**, 63–64 (1946)
166. LUDEWIG, S., AND CHANUTIN, A., *Endocrinology*, **41**, 135–43 (1947)
167. LUSK, G., *The Elements of the Science of Nutrition*, 4th Ed., 276–308 (W. B. Saunders Company, Philadelphia, Pa., 1928)
168. MAN, E. B., CULOTTA, C. S., SIGFRIED, D. A., AND STILSON, C., *J. Pediat.*, **31**, 154–60 (1947)
169. MARCUS, H., AND GLOTZER, S., *N. Y. State J. Med.*, **48**, 1461–64 (1948)
170. MARSH, J. B., AND DRABKIN, D. L., *J. Biol. Chem.*, **168**, 61–73 (1947)
171. MARTIN, G. J., *Am. J. Digestive Diseases*, **14**, 341–42 (1947)
172. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARAMELLI, L. C., LI, C. H., AND EVANS, H. M., *J. Biol. Chem.*, **169**, 223–24 (1947)

173. MARX, W., MESERVE, E., AND DEUEL, H., J., JR., *Proc. Soc. Exptl. Biol. Med.*, **67**, 385–87 (1948)
174. MCCLENDON, J. F., AND FOSTER, W. C., *J. Clin. Endocrinol.*, **7**, 714–15 (1947)
175. MCCLENDON, J. F., FOSTER, W. C., AND CAVETT, J. W., *Endocrinology*, **42**, 168–73 (1948)
176. MCCULLAGH, E. P., HIBBS, R. E., AND SCHNEIDER, R. W., *Am. J. Med. Sci.*, **214**, 545–52 (1947)
177. MCDONALD, D. F., AND ODELL, L. D., *J. Clin. Endocrinol.*, **7**, 535–42 (1947)
178. MCGINTY, D. A., RAWSON, R. W., FLUHARTY, R. G., WILSON, M., RIDDELL, C., AND YEE, H., *J. Pharmacol. Exptl. Therap.*, **93**, 246–57 (1948)
179. MCSHAN, W. H., ERWAY, W. F., AND MEYER, R. K., *Arch. Biochem.*, **16**, 379–87 (1948)
180. MCSHAN, W. H., MEYER, R. K., AND ERWAY, W. F., *Arch. Biochem.*, **15**, 99–110 (1947)
181. MEYER, R. K., SOUKUP, S. W., MCSHAN, W. H., AND BIDDULPH, C., *Endocrinology*, **41**, 35–44 (1947)
182. MEYERHOF, O., AND RANDALL, L. O., *Arch. Biochem.*, **17**, 171–82 (1948)
183. MILLER, D. C., AND EVERETT, J. W., *Endocrinology*, **42**, 421–23 (1948)
184. MILLER, W. H., ROBLIN, R. O., JR., AND ASTWOOD, E. B., *J. Am. Chem. Soc.*, **67**, 2201–4 (1945)
185. MOEHLIG, R. C., *J. Clin. Endocrinol.*, **7**, 134–51 (1947)
186. MOEHLIG, R. C., AND ABBOTT, H. L., *J. Am. Med. Assoc.*, **134**, 1521–24 (1947)
187. MOSZKOWSKA, A., *Ann. endocrinol. (Paris)*, **8**, 241–47 (1947)
188. MOUNT, L. E., *J. Endocrinol.*, **5**, 243–46 (1948)
189. MOYA, F., PRADO, J. L., RODRIGUEZ, R., SAVARD, K., AND SELYE, H., *Endocrinology*, **42**, 223–29 (1948)
190. NELSON, R. A., *Am. J. Digestive Diseases*, **14**, 352–59 (1947)
191. OLSEN, N. S., AND KLEIN, J. R., *Arch. Biochem.*, **13**, 343–47 (1947)
192. OSTER, R. H., AND SMITH, D. C., *Am. J. Physiol.*, **150**, 321–24 (1947)
193. PERSIKE, E. C., *Endocrinology*, **42**, 356–62 (1948)
194. PERSIKE, E. C., *Endocrinology*, **42**, 363–69 (1948)
195. PETERS, J. P., AND MAN, E. B., *J. Clin. Invest.*, **27**, 397–405 (1948)
196. PETERS, J. P., MAN, E. B., AND HEINEMANN, M., *Yale J. Biol. and Med.*, **20**, 449–63 (1948)
197. PITT RIVERS, R., AND LERMAN, J., *J. Endocrinol.*, **5**, 223–28 (1948)
198. PONZ, F., *Rev. españ. fisiol.*, **1**, 173–85 (1945); *Chem. Abstracts*, **41**, 4519 (1947)
199. PRICE, W. H., CORI, C. F., AND COLOWICK, S. P., *J. Biol. Chem.*, **160**, 633–34 (1945)
200. PRITCHARD, J. J., *J. Anat.*, **81**, 352–64 (1947)
201. PURVES, H. D., AND GRIESBACH, W. E., *Brit. J. Exptl. Path.*, **28**, 46–53 (1947)
202. QUIMBY, E. H., AND MCCUNE, D. J., *Radiology*, **49**, 201–5 (1947)
203. RAWSON, R. W., MCGINTY, D. A., PEACOCK, W., MERRILL, P., WILSON, M., AND LOCKHART, H., *J. Pharmacol. Exptl. Therap.*, **93**, 240–45 (1948)
204. RAWSON, R. W., AND MCARTHUR, J. W., *J. Clin. Endocrinol.*, **7**, 235–63 (1947)
205. REID, C., *J. Physiol. (London)*, **106**, 26P-27P (1947)
206. REID, C., *J. Physiol. (London)*, **106**, 27P (1947)
207. REID, G., *Australian J. Exptl. Biol. Med. Sci.*, **26**, 107–21 (1948)

208. REISS, M., *J. Endocrinol.*, **5**, xxxv (1947)
209. REISS, M., *J. Endocrinol.*, **5**, xli-xlv (1947)
210. REISS, M., AND REES, D. S., *Endocrinology*, **41**, 437–40 (1947)
211. ŘEŘÁBEK, J., AND ŘEŘÁBEK, E., *Acta Physiol. Scand.*, **14**, 276–90 (1947)
212. RIESSER, O., *Biochim. et Biophys. Acta*, **1**, 208–33 (1947)
213. ROY, A., *J. Endocrinol.*, **5**, xxxv (1947)
214. RUNE FRISK, A., AND JOSEFSSON, E., *Acta Med. Scand.*, Suppl. 196, 85–91 (1947)
215. SADHU, D. P., *Coll. Agr. Research Bull.*, No. 408 (Univ. of Missouri, Columbia, Missouri, 1947)
216. SADHU, D. P., *Am. J. Physiol.*, **152**, 150–56 (1948)
217. SADHU, D. P., *Am. J. Physiol.*, **152**, 263–66 (1948)
218. SADHU, D. P., AND BRODY, S., *Am. J. Physiol.*, **151**, 130–33 (1947)
219. SADHU, D. P., AND BRODY, S., *Am. J. Physiol.*, **151**, 342–44 (1947)
220. SAYERS, G., SAYERS, M. A., LIANG, T. Y., AND LONG, C. N. H., *Endocrinology*, **37**, 96–110 (1945)
221. SAYERS, G., SAYERS, M. A., LIANG, T. Y., AND LONG, C. N. H., *Endocrinology*, **38**, 1–9 (1946)
222. SAYERS, M. A., SAYERS, G., AND WOODBURY, L. A., *Endocrinology*, **42**, 379–93 (1948)
223. SCHIFFER, F., AND WERTHEIMER, E., *J. Endocrinol.*, **5**, 147–51 (1947)
224. SCHWEIZER, W., *J. Physiol.* (*London*), **106**, 167–76 (1947)
225. SHERRY, S., AND RALLI, E. P., *J. Clin. Invest.*, **29**, 217–25 (1948)
226. SHIPLEY, R. A., CHUDZEK, E. B., AND GYÖRGY, P., *Arch. Biochem.*, **16**, 301–7 (1948)
227. SIMKINS, S., *J. Clin. Endocrinol.*, **7**, 574–85 (1947)
228. SIMPSON, B. W., *Biochem. J.*, **41**, xlv–xlvi (1947)
229. SMITH, A. U., *J. Endocrinol.*, **5**, lxiv (1947)
230. SMITH, A. U., EMMENS, C. W., AND PARKES, A. S., *J. Endocrinol.*, **5**, 186–205 (1947)
231. SOMOGYI, M., *J. Biol. Chem.*, **174**, 189–200 (1948)
232. SOMOGYI, M., *J. Biol. Chem.*, **174**, 597–603 (1948)
233. SOULAIRAC, A., *Ann. endocrinol.* (*Paris*), **8**, 377–93 (1947)
234. SOULAIRAC, A., AND DESCLAUX, P., *Ann. endocrinol.* (*Paris*), **8**, 343–46 (1947)
235. SOVIOTTI, G., *Farm. sci. e tec.* (*Pavia*), **2**, 455–57 (1947); *Chem. Abstracts*, **42**, 3076 (1948)
236. SPRAGUE, R. G., GASTINEAU, C. F., MASON, H. L., AND POWER, M. H., *Am. J. Med.*, **4**, 175–85 (1948)
237. STADIE, W. C., HAUGAARD, N., AND PERLMUTTER, M., *J. Biol. Chem.*, **171**, 419–29 (1947)
238. STADIE, W. C., HAUGAARD, N., AND PERLMUTTER, M., *J. Biol. Chem.*, **172**, 567–77 (1948)
239. STADIE, W. C., AND ZAPP, J. A., JR., *J. Biol. Chem.*, **170**, 55–65 (1947)
240. STAFFORD, R. O., MCSHAN, W. H., AND MEYER, R. K., *Endocrinology*, **41**, 45–54 (1947)
241. STANLEY, M. M., AND ASTWOOD, E. B., *Endocrinology*, **41**, 66–84 (1947)
242. STANLEY, M. M., AND ASTWOOD, E. B., *Endocrinology*, **42**, 107–23 (1948)

243. STEPHENSON, H. U., JR., AND MCNAMARA, W. L., *Am. J. Med. Sci.*, **215**, 381–97 (1948)
244. STETTEN, D., JR., *N. Y. State J. Med.*, **47**, 1991–96 (1947)
245. STOERK, H. C., JOHN, H. M., AND EISEN, H. N., *Proc. Soc. Exptl. Biol. Med.*, **66**, 25–28 (1947)
246. SURTSHIN, A., RODBARD, S., AND KATZ, L. N., *Am. J. Physiol.*, **152**, 623–32 (1948)
247. SUTHERLAND, E. W., AND CORI, C. F., *J. Biol. Chem.*, **172**, 737–49 (1948)
248. SWENSON, R. E., AND CURTIS, G. M., *Am. Practitioner*, **10**, 671–73 (1948)
249. TALBOT, N. B., ALBRIGHT, F., SALTZMAN, A. H., ZYGMUNTOWICZ, A., AND WIXOM, R., *J. Clin. Endocrinol.*, **7**, 331–50 (1947)
250. TAUROG, A., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **169**, 49–56 (1947)
251. TAUROG, A., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **171**, 439–40 (1947)
252. TAUROG, A., CHAIKOFF, I. L., AND FELLER, D. D., *J. Biol. Chem.*, **171**, 189–201 (1947)
253. TEJNING, S., *Acta Med. Scand.*, Suppl. 198, 1–154 (1947)
254. THOMPSON, W. O., THOMPSON, P. K., AND MANDERNACH, D. M., *Western J. Surg. Obstet. Gynecol.*, **56**, 270–77 (1948)
255. TIPTON, S. R., LEATH, M. J., TIPTON, I. H., AND NIXON, W. L., *Am. J. Physiol.*, **145**, 693–98 (1946)
256. TISSIÈRES, A., *Arch. intern. physiol.*, **54**, 305–13 (1946)
257. TISSIÈRES, A., *Arch. intern. physiol.*, **55**, 252–57 (1948)
258. TODD, W. R., BARNES, J. M., AND CUNNINGHAM, L., *Arch. Biochem.*, **13**, 261–64 (1947)
259. TRUCCO, R. E., CAPUTTO, R., LELOIR, L. F., AND MITTLEMAN, N., *Arch. Biochem.*, **18**, 137–46 (1948)
260. TWEEDY, W. R., CHILCOTE, M. E., AND PATRAS, M. C., *J. Biol. Chem.*, **168**, 597–610 (1947)
261. UCKO, H., *J. Clin. Endocrinol.*, **7**, 820–27 (1947)
262. VAIL, V. N., AND KOCHAKIAN, C. D., *Am. J. Physiol.*, **150**, 580–87 (1947)
263. VANDENBROECK, J., AND FÉRIN, J., *Ann. endocrinol. (Paris)*, **8**, 366–69 (1947)
264. VANDERLAAN, W. P., AND BISSELL, A., *Endocrinology*, **39**, 157–60 (1946)
265. VENNING, E. H., AND BROWNE, J. S. L., *J. Clin. Endocrinol.*, **7**, 79–101 (1947)
266. VERNE, J., AND HÉBERT, S., *Compt. rend. soc. biol.*, **142**, 300–1 (1948)
267. VIVONE, F. R., ETIENNE, L., AND TRUCCO, E., *Semana méd. (Buenos Aires)*, **II**, 1–6 (1947); *Chem. Abstracts*, **41**, 6969 (1947)
268. VOGT, M., *J. Endocrinol.*, **5**, lvii–lx (1947)
269. VOGT, M., *J. Physiol. (London)*, **106**, 394–404 (1947)
270. VOGT, M., *J. Physiol. (London)*, **107**, 239–43 (1948)
271. VUYLSTEKE, C. A., *Arch. intern. pharmacodynamie*, **75**, 439–43 (1948)
272. WALSH, F. B., AND HOWARD, J. E., *J. Clin. Endocrinol.*, **7**, 644–52 (1947)
273. WATSON, E. M., AND PEARCE, R. H., *Am. J. Clin. Path.*, **17**, 507–12 (1947)
274. WEIL, R., AND STETTEN, D., JR., *J. Biol. Chem.*, **168**, 129–32 (1947)
275. WHITE, A., AND DOUGHERTY, T. F., *Ann. N. Y. Acad. Sci.*, **46**, 859–82 (1946)
276. WHITE, A., AND DOUGHERTY, T. F., *Endocrinology*, **41**, 230–42 (1947)
277. WHITE, H. L., HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **151**, 239–44 (1947)

278. WHITELAW, M. J., *J. Clin. Endocrinol.*, **7**, 767–73 (1947)
279. WIESE, C., DEUEL, H. J., JR., AND MEHL, J. W., *Proc. Soc. Exptl. Biol. Med.*, **66**, 213–14 (1947)
280. WILDER, J., *Am. J. Digestive Diseases*, **15**, 183–94 (1948)
281. WILLIAMSON, M. B., *Proc. Soc. Exptl. Biol. Med.*, **66**, 621–23 (1947)
282. WINKLER, A. W., MAN, E. B., AND DANOWSKI, T. S., *J. Clin. Invest.*, **26**, 446–52 (1947)
283. WINNICK, T., FRIEDBERG, F., AND GREENBERG, D. M., *J. Biol. Chem.*, **173**, 189–97 (1948)
284. WOLFF, J., AND CHAIKOFF, I. L., *Endocrinology*, **41**, 295–98 (1947)
285. WOLFF, J., AND CHAIKOFF, I. L., *J. Biol. Chem.*, **174**, 555–64 (1948)
286. WOLFF, J., AND CHAIKOFF, I. L., *Endocrinology*, **42**, 468–71 (1948)
287. YOUNG, F. G., *J. Endocrinol.*, **5**, xlv–lii (1947)
288. ZIERLER, K. L., AND LILIENTHAL, J. L., *Am. J. Med.*, **4**, 186–92 (1948)

LIVER[1]

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The liver, in contrast to the kidney, is said to be "one of the simplest glandular structures in the body" (1). Nevertheless, great numbers of investigators encounter difficulty in the analysis of its many functions.

Clinical interest in hepatic physiology has increased in recent years due, in part, to the greater incidence of the disease virus hepatitis. More accurate diagnoses through the use of multiple liver function tests and needle biopsies are now possible. The therapeutic results have improved because of greater attention to nutrition. Monographs by Schiff (2), Movitt (3), and Himsworth (4) and reviews by Young (5) and Weir (6) summarize much of the current data. Multiple liver function tests (7), clinical employment of the galactose tolerance test (8, 9, 10), and the inadequacy of the glucose tolerance test for diagnosis of hepatic disease (11, 12) have received comment. The variations and difficulties encountered with the hippuric acid synthesis as a test of liver function were reported by Sherlock (13), and Snapper & Saltzman (14) discussed the results with their new benzoyl glucoronate excretion test.

The two most useful clinical biochemical tests currently available for recognizing parenchymal liver damage, particularly that due to virus hepatitis, are the cephalin cholesterol flocculation test introduced by Hanger and the thymol turbidity test of Maclagan. Recent clinical reports (15 to 18) discuss their employment. The mechanisms involved in the production of turbidity by the thymol reagent have been studied by Cohen & Thompson (19), Maclagan & Bunn (20), and by Kunkel & Hoaglund (21).

Much of the pertinent literature as to the relationship of the liver and the plasma proteins is cited in the extensive review by Metcoff & Stare (22). Martin (23) and Havens & Williams (24) studied the serum protein changes in acute hepatitis. Dent (25) employed paper partition chromatography to study the urinary excretion of amino acids in patients with liver disease; Frankl,

[1] This review includes papers published during the period July 1, 1945 to July 1, 1948; no pretext is made that all of the extensive literature of that period has been surveyed.

Martin & Dunn (26) employed a microbiological assay technique for the same purpose. Lewis, Taylor & Davidson (27) did not find the amino acid tolerance sufficiently altered in patients with severe liver dysfunction to employ this procedure as a functional test.

Serum cholinesterase regeneration rates have been studied in patients with liver disease by Wescoe *et al.* (28). Sawyer & Everett (29) concluded that the liver was the site of synthesis of the serum nonspecific cholinesterase in the rat. Defective formation of plasma esterase paralleled the defective formation of plasma albumin in patients with liver disease studied by Kunkel & Ward (30). Balfour (31) employed radiophosphorus in a study of the phospholipids and observed that high plasma levels in patients with hepatic disorders was associated with overproduction by the liver.

Nutritional relationships.—Nutritional deficiencies as a cause of hepatic dysfunction in man attracts considerable interest (32, 33 34); Himsworth (4) has discussed the subject in detail. Needle biopsy studies, performed upon individuals suffering from severe malnutrition, are of unusual value in determining what structural changes occur. Von Falkenhausen & Gaida (35) and Sherlock & Walshe (36) have each reported such studies in twenty cases. Surprisingly slight histological changes were noted and no signs of fatty changes or cirrhosis were found. The deposition of iron in such livers was not as extensive as that described by Gillman & Gillman (37) in the liver biopsies performed on malnourished South African natives.

Antecedent malnutrition might be expected to increase the severity of virus hepatitis; studies in Burma by Stokes & Miller (38) and in India by Damodaran (39) did not demonstrate this. The fallacy that a low fat diet was essential for the treatment of infectious hepatitis has been dispelled by the studies of Wilson, Pollack & Harris (40) and Hoaglund and associates (41).

The lipotropic factors, in particular methionine, have been the subject of a great deal of clinical investigation. Eddy (42) advocates the use of extra methionine in the prevention and treatment of hepatic injury due to industrial poisons. Two widely quoted papers [Beattie *et al.* (43) and Eddy (44)] advocate the employment of methionine in the treatment of liver damage due to carbon tetrachloride. Drill and his co-workers (45) offer critical comment on these two reports. The addition of choline or methionine as a supplement to an already adequate diet has not

been shown to be of benefit where liver damage is the result of an infectious agent (46, 47, 48). The status of methionine in clinical practice has been reviewed by the Council on Pharmacy and Chemistry of the American Medical Association (49). Beams & Endicott (50) felt that the improved histologic changes in the livers in nine cirrhotic patients treated with an adequate diet, yeast, crude liver extract, and methionine was due to the methionine. Five additional cirrhotic patients received a similar regime except for the additional methionine; one showed histologic improvement. Studies of the urinary excretion of methionine in normals (51) and in patients with liver disease (52, 53) and of plasma levels following intravenous and oral administration (54, 55) have been reported. The studies of Johnson and his co-workers (56) and of Cox and his co-workers (57) demonstrated the lower requirements of humans for the sulfur-containing amino acids and the absence of a protein-sparing effect, a finding noted by Riegel and her associates (58).

The effect of a nutritional program in increasing the life expectancy of patients with cirrhosis was observed by Kimball & Chapple (59) and by Patek (60), but not by Wade (61). The very real importance of the factor of appetite in experimental and clinical liver dysfunction, emphasized by Freeman (62), is well recognized by the investigators at the Rockefeller Institute (63). It warrants still wider appreciation.

Experimental Liver Injury

Chemical agents.—Casals & Olitsky (64) adapted the bromosulfalein test for evaluation of chemical liver injury in mice. Svirbely, Monaco & Alford (65) found this dye test gave the earliest evidence of liver damage when xylidine was employed as the toxic agent. Li & Freeman (66, 67) and their associates Hough & Gunn (68) studied the influence of diet on the toxicity of benzene. Ashworth & Mason (69) found that the hepatic injury produced by a toxic substance present in blue green algae (*Microcystis aeruginosa*) was distinguished by the remarkable rapidity of the development of the lesions.

Ashworth (70) reported that alcohol produced fatty livers in rats maintained on an adequate diet. Fatty infiltration was estimated by histologic examination. This is an extremely important subject and deserves further investigation since the pathogenesis

of cirrhosis in the chronic alcoholic [only 8 per cent develop cirrhosis (71)] is so poorly understood. Rogers (72) has studied hepatic changes in normal and allergic rabbits as influenced by alcohol. Experimentally induced hepatic changes in rabbits are often difficult to evaluate as Ashworth (70) points out.

Rosin & Doljanski (73, 74) have described early histologic changes in the livers of rats injured by allyl formate and by carbon tetrachloride. The latter agent was employed by Williams & Frantz (75) in their studies of liver injury. A vital staining technique was utilized. Glynn & Himsworth (76) believe much of the hepatic damage by carbon tetrachloride can be accounted for by the alterations in the circulation that this agent produces. The thymol barbital turbidity test was employed by McCord, Sterner, Kline & Williams (77) and by Brieger & Friedman (78) for the early detection of carbon tetrachloride hepatic injury in animals. A number of observers (79 to 85) have investigated the action of dietary substances in protecting the liver against the injury provoked by carbon tetrachloride. The liver of a well-fed, normal animal probably offers the maximal possible resistance to toxic agents. It is doubtful that the addition of a single nutritional substance to an already adequate diet will augment this resistance. Drill, Loomis & Belford (45) have summarized much of the current data on the hepato-toxic effects of carbon tetrachloride. Sellers, Lucas & Best (86) studied the influence of lipotropic agents in young adult rats recovering from a moderate degree of cirrhosis produced by the administration of carbon tetrachloride. The presence of choline, or its precursor methionine, was found to be essential for repair of the damaged liver; but the therapeutic effect of an already adequate diet was not enhanced by the addition of lipotropic agents. These investigators noted the apparent disappearance of fibrous tissue from the cirrhotic livers, a process which Steinberg & Martin (87) were able to demonstrate by means of x-ray visualization following thorotrast injection. Morrione (88) studied the absorption of scar tissue in experimental cirrhosis by a quantitative analysis of the collagen content. These important studies indicate the potential reversibility of experimental cirrhosis, a phenomenon that can occur providing exposure to the toxic agent ceases. Warren & Wahi (89) applied the quantitative analysis of fibrous tissue to human pathologic livers. These studies were made upon necropsy material.

The methods available do not permit estimations on fragments as minute as those obtained by needle biopsy, although Bondy, Sheldon & Evans (90) employed such specimens for quantitative analysis of glycogen.

Cincophen toxicity was the subject of an extensive review by Hueper (91), who noted that despite a great deal of experimental work, the nature of cincophen hepatotoxicosis has not been elucidated. Baxter (92, 93, 94) studied the mechanisms of hepatic injury produced by the administration of pyridine.

Rubarth (95) reported his extensive investigations in Stockholm on a virus disease producing liver lesions in dogs.

Dietary liver damage.—This important subject deserves more comment than this review permits. The subject is reviewed by Witts (96), by Glynn (97), and by Himsworth (4). Rhadhakrishna Rao, in a succinct note (98), discusses the problem of dietetic hepatic lesions and indicates some of the variations in results that have been observed.

Best and co-workers (99, 100, 101) have presented further data bearing on the lipotropic factors and the problem of the development of fatty infiltration of the liver. A review article by Best (102) deals with the factors affecting fat transport. Montgomery, Entenman & Chaikoff (103) found the pancreatic juice to be a rich source of the antifatty liver factor. It is their belief that this factor is identical with that present in the raw pancreas customarily used, with insulin, to maintain depancreatized dogs. Chaikoff, Entenman & Montgomery (104) presented evidence that the defect in the depancreatized dog, maintained with insulin, lies in the mechanism whereby the methionine of ingested protein is made available for lipotropic purposes. Two recent papers from that laboratory (105, 106) deal with the relationship of hypophysectomy and thyroidectomy to the development of fatty livers. Clark, Eilert & Dragstedt (107) and Eilert & Dragstedt (108) have published further studies on the lipotropic action of lipocaic. Canepa & Ivy (109) compared the lipotropic activity of Dragstedt and Chaikoff's pancreatic extracts. On the basis of results obtained following the parenteral administration of these extracts to rats with fatty livers, they concluded that the lipotropic principle present in each was not the same.

Li & Freeman (110) investigated the effects of protein deficiency and cholesterol feeding in relation to fatty infiltration of the liver

in dogs. The fat that accumulates in the liver of a protein-deficient dog was felt to be largely of exogenous origin. Groen (111) studied fatty livers in dogs produced by an abnormally high fat diet. Campbell's studies (112) related to the manner in which insulin affected the increase in liver fat produced by anterior pituitary extracts. Miller and associates (113) were unable to detect functional hepatic changes, as judged by the results obtained with the bilirubin clearance test, in protein-depleted dogs. The changes in hepatic function observed in chronic vitamin B complex-deficient dogs by Drill & Loomis (114) were quite minimal.

Rich, Berthrong & Germuth (115) demonstrated that fat-laden liver cells had very poor regenerative ability. Mitotic figure counts were performed and the stimulus to regeneration produced by partial hepatectomy in the rat was evaluated. The authors believe the impairment of the regenerative capacity of the fatty liver may play a significant role in the pathogenesis of cirrhosis under such conditions. Wilson & LeDuc (116) studied mitotic rates in mouse livers as influenced by the intraperitoneal injection of liver and other substances. Kosterlitz (117) summarized his studies on the influence of dietary protein on the composition and structure of the liver cell. The regeneration of liver protein has been used by Harrison & Long (118) in nutritional studies. The substitution of pure amino acids for dietary protein in the rat was investigated by Rose, Machella & György (119). Even though an adequate content of methionine was given, liver fat was found to be increased.

The observations of Schwarz (120) that hepatic lesions developing in rats fed a special casein diet were preventable by supplements of tocopherol await further confirmation. Himsworth (4) stated that an inadequate supply of tocopherol may sensitize the animal to a deficiency of cystine. Neuberger & Webster (121) believed that the inclusion of tocopherol in their diets, employed to study alkaptonuria in rats, may have been a factor in their failure to observe massive hepatic necrosis in these studies. The diets previously employed by Glynn, Himsworth & Neuberger (122), when massive hepatic necrosis was observed, apparently did not contain tocopherol.

Hepatectomy.—A number of investigators have employed partial or complete hepatectomy in the study of the physiology of the liver. Reinhardt & Bazell (123) described their technique for a one stage functional hepatectomy in the rat. The influence of hepatec-

tomy on the protein and prothrombin content of the plasma have been described (124, 125).

Partial hepatectomy was employed by Oppenheimer & Flock (126) to study the alkaline phosphatase content of plasma and liver and by Drabkin (127) to study the cytochrome-*c* metabolism. Vars & Gurd (128) studied the role of dietary protein in experimental liver regeneration. Gurd, Vars & Ravdin (129) determined the composition of the regenerated portion of the liver in the rat following removal of approximately 70 per cent of this organ. Even in the face of continued protein starvation, rats previously depleted of protein exhibited regeneration, though not to the extent that an adequate diet permitted. Drabkin (130) observed that regeneration proceeded reasonably well even in thyroidectomized rats. Observations on the powerful stimulus to regeneration that partial hepatectomy provokes has been previously cited [Rich *et al.* (115)]. Denton & Ivy (131) studied the effect of feeding liver on the rate of restoration of the hepatic tissue. Preliminary reports by Newman & Grossman (132) and by Vars & Friedgood (133) also relate to this subject. Rittenberg, Sproul & Shemin (134) employed glycine containing N^{15} in similar studies.

Phosphatase.—Wachstein (135) and Wachstein & Zak (136, 137) studied the histochemical distribution of phosphatase in the liver under experimental conditions and in human livers obtained at necropsy. Sherlock & Walshe (138) employed fresh human liver tissue, obtained by needle biopsy, for histological and microchemical studies. Deane (139) published an extensive study on the distribution of phosphatases in various tissues. Jacoby (140) believes the histochemical method for the demonstration of phosphatase is superior to older methods for the delineation of the bile capillaries. Jalling and his associates (141, 142) performed quantitative studies of tissue phosphatase content following experimental ligation of the common bile duct. A similar investigation was reported by Gad (143). The high content of phosphatase in the intestinal mucosa, noted by these observers and by Dalgard (144), has been investigated by Flock & Bollman (145). The latter studied intestinal lymph for its phosphatase content and found as great an increase after a fat-free meal as after a fatty meal.

Estrogens.—Clinical interest in the relationship of the liver to the physiology of estrogenic substances has increased in recent years. A malignant form of hepatitis occurring in women past the

age of the menopause has been observed in Denmark (146, 147). Various manifestations suggesting endocrinologic disturbances in chronic forms of liver disease are reviewed by Bean (148), by Lloyd & Williams (149), and by Rather (150) and have been studied experimentally (151). The implication that the gynecomastia observed in malnutrition may be related to disturbed hepatic function has received comment (152 to 155). Gilder & Hoaglund (156) studied the urinary excretion of estrogens in infectious hepatitis. Zondek & Black (157), studying estrone clearance in infectious hepatitis, found that the human liver could inactivate estrogen despite the presence of severe functional impairment. Only those patients who demonstrated failure of urea synthesis, usually one of the last functions of the liver to fail, also failed to inactivate estrogen. The observations of Hooker, Drill & Pfeiffer (158) in monkeys also indicated that estrogen inactivation by the liver varies in different species. Emery & Joyce (159) employed interruption of the common bile duct to study the enterohepatic circulation of the estrogens, and others (160, 161) have studied the effects of partial hepatectomy on the inactivation of estrogens. Other *in vivo* and *in vitro* studies in this connection have been reported (162, 163): Drill & Pfeiffer (164) concluded from their studies that the effect of vitamin B complex deficiency in producing a failure of the liver to inactivate estrone is due to the associated inanition and not to the vitamin deficiency per se. György, Rose & Shipley (165) have observed that estrone augmented the lipotropic effect of methionine in rats.

Water Balance

The role played by the liver in the regulation of fluid balance has received considerable investigation. The subject is discussed by Pick (166) and clinical investigations by Labby & Hoaglund (167, 168), Perera (169), and Layne & Schemm (170) relate to this. The important study of Ralli *et al.* (171) demonstrated the relationship of an antidiuretic factor to the formation of ascites. Leslie & Ralli (172) have presented experimental data indicating the role played by an antidiuretic substance in the presence of liver damage. Recent preliminary reports (173, 174) also concern the relationship of antidiuretic substances to hepatic function. Higgins and co-workers (175) have discussed the subject of ascites in patients with chronic liver disease. Although they found the

colloidal osmotic pressure, as reflected by the plasma protein level, a useful diagnostic aid in the presence of ascites, the correlation was not absolute. Drainage of ascitic fluid into the abdominal wall has received attention (176, 177).

The availability of human serum albumin for clinical investigation has afforded several groups an opportunity to study in detail the relationship of the plasma protein level to the accumulation of ascites (178 to 181). Armstrong (182) has reviewed many of the recent investigations.

The observations of Bolton (183) on the role that hepatic lymph production plays in the formation of ascites is seldom mentioned in recent articles that discuss the plasma protein levels, portal venous pressure, and the failure of the damaged liver to inactivate antidiuretic substances. Grindlay and his associates (184, 185, 186) have recently investigated this subject by techniques that permit the collection of lymph from the liver and the thoracic duct in intact animals. A greatly increased flow of hepatic lymph was observed in dogs with cirrhosis induced by carbon tetrachloride and in dogs with chronic passive congestion of the liver.

Hepatic Circulation

Knisely, Bloch & Warner (187) described their observations of the circulation in the living frog. Dock (1) reviewed some aspects of hepatic circulation. By the ingenious method of injecting glass beads of known size into the portal vein, Prinzmetal *et al.* (188) have demonstrated venous-venous anastomoses in the liver. A portal anastomotic vein has been employed in absorption studies in man (189).

A great deal of clinical interest in hepatic circulation has developed in recent years as the result of the performance of portocaval anastomoses by Whipple (190), Blakemore (191), Blalock (192), and Linton (193). The existence of esophageal varices and their ever present threat to the life of patients with liver disease has led to various surgical attacks on the problem. Gastric resection has been performed (194, 195). Experimental attempts to measure the level of the portal vein pressure (196), to produce portal hypertension (197), and to resect the portal vein (198) have been reported. Bollman (199) reviewed the experimental methods of altering hepatic circulation, and Drill (200) studied the interesting phenomenon of meat intoxication in dogs with Eck

fistulae. A detailed account of the portal pressure gradients under various experimental conditions was presented by Wiggers, Opdyke & Johnson (201).

The important role of the liver in shock has received much attention in the last few years. The subject has been reviewed by Wilhelmi (202). Selkurt, Alexander & Patterson (203), Fine, Seligman & Frank (204), and Shorr (205) have recently published reports, and preliminary communications (206, 207) have appeared.

The measurement of hepatic blood flow in man has become possible since the demonstration by Bradley (208, 209) that hepatic vein catheterization and measurement of the rate of the removal of infused bromosulfalein can be employed for such calculations. Values so obtained averaged 1,440 cc. per min. per 1.73 square meters of body surface in the adult. This method has been employed to measure liver blood flow in pregnancy (210), in cirrhosis (211), and to determine the effect of exercise and posture on blood flow through the liver (212). The studies of Myers (213) revealed the validity of the basic assumption of the bromosulfalein extraction method for this purpose since the figures contrasted well with those obtained when urea production by the liver was measured and employed for similar calculations. Lipscomb & Crandall (214) utilized the urea method for the determination of hepatic blood flow in dogs. Cohn, Levine & Streicher (215) believed the extrahepatic removal of bromosulfalein, in the dog at least, cast doubt on the validity of this method. Mason, Hawley & Smith (216) found this dye satisfactory when employed to measure the functional hepatic mass in dogs.

Pigment Metabolism

Watson (217) reviewed the recent data on the behavior of the serum bilirubin and presented data on the "one minute bilirubin," the term employed to designate the prompt direct reacting component. Reference is also made to the renal threshold for bilirubin which, as Neefe & Reinhold (218) observed, is not a fixed level. With (219, 220) has reviewed a number of his published papers on the problem of bilirubin production and elimination. This subject is also reviewed by Enachesco and his co-workers (221). With (222) and Lups & Meijer (223) have studied the occurrence of a yellow pigment other than carotene in the sera of patients that

fail to give a diazo reaction. With believes the pigment may be related to xanthopterin found in the plasma of hepatectomized dogs but offers no proof of this.

The van den Bergh reaction has been reinvestigated by With (224). Gray (225) reviewed his studies with Whidborne (226) and recommends that the terms direct and indirect bilirubin should be abandoned and the term direct-indirect quotient be substituted. The very real practical value of the van den Bergh reaction in distinguishing retention and regurgitation jaundice will doubtless dictate its continued use in the clinic. Martin (227) has observed that bilirubin may be bound to the alpha globulins in the blood stream as well as to the albumin fraction.

Loewy & Freeman (228) claim that a portion of the hyperbilirubinemia of the newborn is related to hemolysis of erythrocytes resulting from the ingestion of fat by the infant. Although the average bilirubin value of the newborns fed a fat-free formula was somewhat lower, the range of the individual values was nearly as great as the control group.

With (229, 230) found the urobilinogen tolerance test to be of little practical value as a measure of liver function. Watson & Hawkinson (231) have reported further experiences with their simple quantitative Ehrlich reaction. The urobilinogen in normals and in cirrhotics has been studied by Pellegrino *et al.* (232). Naumann (233) described techniques for urobilin determination to avoid interference by other fluorescent materials.

Watson & Larson (234) reviewed their experiences with the detection of coproporphyrin in the urine as an indication of hepatic dysfunction. Dent & Rimington (235) have observed porphyrinuria in rats fed oxidized casein.

The studies of London and co-workers (236) on the origin of stercobilin in humans indicate that the present concepts of pigment metabolism may undergo some modifications in the future. Glycine labeled with N^{15} was fed to human subjects; this resulted in the incorporation of N^{15} in the heme of red blood cells during hematopoiesis. Destruction of such cells in seventy to one hundred and twenty-eight days permitted observation of the process of hemoglobin degradation. The data indicated that a significant proportion of normal stercobilin results from sources other than the destruction of hemoglobin.

Biliary Tract

Scott's observations (237) indicate the essential role that bile plays in the absorption of the fat soluble vitamins. Boyd and associates (238) emphasized the changes in the composition of bile that occurred in chronic bile fistula animals as the loss of inorganic salts continues. Irvin, Johnston & Sharp (239) employed cholates, normally absent from the bile of hogs, to trace the enterohepatic circulation of the bile acids in these animals. Johnston & Irvin (240) later reported a detailed study of the biliary excretion of bile acids in eleven patients whose common bile duct obstruction had been released by surgical means. With (241) studied the output of bilirubin and urobilin in human fistula bile. Snape, Wirts & Cantarow (242) compared the merits of a modified Rous-McMaster and a Thomas intestinal fistula type of external biliary fistula. The latter was found to be superior for the study of liver function where one desires bile collections.

Grafflin (243) studied in detail the excretion of fluorescein, as observed *in vivo* in frogs, by means of fluorescent microscopy. The excretion of the dye, T-1824, in the bile was described by Miller (244). Mixer, Rigler & Gonzalez-Oddone (245) observed considerable biliary regurgitation during experimental cholangiographic studies. Halpert, Russo & Cushing (246) state that on the basis of study of twelve normal subjects the diminution in the size of the human gall bladder, as visualized roentgenographically after a fatty meal, may be accomplished by selective resorption rather than by evacuation.

LITERATURE CITED

1. DOCK, W., *New Engl. J. Med.*, **236**, 773–82 (1947)
2. SCHIFF, L., *The Differential Diagnosis of Jaundice*, 313 pp. (The Year Book Publishers, Inc., Chicago, 1946)
3. MOVITT, E. R., *Jaundice: Its Pathogenesis and Differential Diagnosis*, 261 pp. (Oxford University Press, New York, N. Y., 1947)
4. HIMSWORTH, H. P., *The Liver and Its Diseases*, 204 pp. (Blackwell Scientific Publications, Oxford, 1947)
5. YOUNG, L. E., *New Engl. J. Med.*, **237**, 225–31 (1947)
6. WEIR, J. F., *J. Am. Med. Assoc.*, **134**, 579–85 (1947)
7. MATEER, J. G., BALTZ, J. I., COMANDURAS, P. D., STEELE, H. H., AND BROUWER, S. W., *Gastroenterology*, **8**, 52–70 (1947)
8. COLCHER, H., PATEK, A. J., JR., AND KENDALL, F. E., *J. Clin. Invest.*, **25**, 768–75 (1946)
9. STENSTAM, T., *Acta Med. Scand.*, **125**, Suppl. 177, 1–155 (1946)
10. ALTHAUSEN, T. L., *Am. J. Med.*, **4**, 208–14 (1948)
11. SWEENEY, J. S., AND FRIEDLANDER R. D., *Am. J. Clin. Path.*, **16**, 150–59 (1946)
12. CAMPBELL, J. A., AND TAGNON, H. J., *New Engl. J. Med.*, **234**, 216–21 (1946)
13. SHERLOCK, S., *Lancet*, **I**, 159–62 (1946)
14. SNAPPER, I., AND SALTZMAN, A., *Am. J. Med.*, **2**, 334–41 (1947)
15. DODDS, D. C., *Calif. Med.*, **66**, 125–27 (1947)
16. MANN, F. D., SNELL, A. M., AND BUTT, H. R., *Gastroenterology*, **9**, 651–55 (1947)
17. NEEFE, J. R., BAHNSON, E. R., AND REINHOLD, J. G., *Gastroenterology*, **9**, 656–71 (1947)
18. SHAY, H., BERK, J. E., AND SIPLET, H., *Gastroenterology*, **9**, 641–50 (1947)
19. COHEN, P. P., AND THOMPSON, F. L., *J. Lab. Clin. Med.*, **32**, 475–80 (1947)
20. MACLAGAN, N. F., AND BUNN, D., *Biochem. J.*, **41**, 580–86 (1947)
21. KUNKEL, H. G., AND HOAGLUND, C. L., *J. Clin. Invest.*, **26**, 1060–71 (1947)
22. METCOFF, J., AND STARE, F. J., *New Engl. J. Med.*, **236**, 26–35, 68–75 (1947)
23. MARTIN, N. H., *Brit. J. Exptl. Path.*, **27**, 369–77 (1946)
24. HAVENS, W. P., JR., AND WILLIAMS, T. L., *J. Clin. Invest.*, **27**, 340–45 (1948)
25. DENT, C. E., *Biochem. J.*, **41**, 240–53 (1947)
26. FRANKL, W., MARTIN, H., AND DUNN, M. S., *Arch. Biochem.*, **13**, 103–12 (1947)
27. LEWIS, J. H., TAYLOR, F. H. L., AND DAVIDSON, C. S., *Am. J. Med. Sci.*, **214**, 656–61 (1947)
28. WESCOE, W. C., HUNT, C. C., RIKER, W. W., AND LITT, I. C., *Am. J. Physiol.*, **149**, 549–51 (1947)
29. SAWYER, C. H., AND EVERETT, J. W., *Am. J. Physiol.*, **148**, 675–83 (1947)
30. KUNKEL, H. G., AND WARD, S. M., *J. Exptl. Med.*, **86**, 325–37 (1947)
31. BALFOUR, W. M., *Gastroenterology*, **9**, 686–94 (1947)
32. MEINENBERG, L. J., AND SNELL, A. M., *Gastroenterology*, **7**, 442–49 (1946)
33. GILLMAN, J., AND GILLMAN, T., *Gastroenterology*, **8**, 19–23 (1947)
34. WATERLOW, J. C., *Proc. Roy. Soc. Medicine*, **40**, 347–51 (1947)
35. VON FALKENHAUSEN AND GAIDA, *Deut. med. Wochschr.*, **72**, 184–86 (1947)

36. SHERLOCK, S., AND WALSHE, V., *Nature*, **161**, 604 (1948)
37. GILLMAN, J., AND GILLMAN, T., *Arch. Path.*, **40**, 239–63 (1945)
38. STOKES, J. F., AND MILLER, A. A., *Quart. J. Med.*, **16**, 211–36 (1947)
39. DAMODARAN, K., *Brit. Med. J.*, **I**, 1079–82 (1948)
40. WILSON, C., POLLACK, M. R., AND HARRIS, A. D., *Lancet*, **I**, 881–83 (1946)
41. HOAGLUND, C. L., LABBY, D. H., KUNKEL, H. G., AND SHANK, R. E., *Am. J. Pub. Health*, **36**, 1287–92 (1946)
42. EDDY, J. H., JR., *Southern Med. J.*, **40**, 171–74 (1947)
43. BEATTIE, J., HERBERT, P. H., WECHTEL, C., AND STEELE, C. W., *Brit. Med. J.*, **I**, 209–11 (1944)
44. EDDY, J. H., JR., *J. Am. Med. Assoc.*, **128**, 994–96 (1945)
45. DRILL, V. A., LOOMIS, T. A., AND BELFORD, J., *J. Ind. Hyg. Toxicol.*, **29**, 180–83 (1947)
46. RICHARDSON, J. S., AND SUFFERN, W. S., *Brit. Med. J.*, **II**, 156–57 (1945)
47. COOK, C. D., AND HOFFBAUER, F. W., *J. Lab. Clin. Med.*, **31**, 56–64 (1946)
48. CAMERON, D. G., AND NEWHOUSE, M. L., *Brit. Med. J.*, **I**, 253 (1948)
49. COUNCIL PHARM. AND CHEM. AM. MED. ASSOC., *J. Am. Med. Assoc.*, **133**, 107 (1947)
50. BEAMS, A. J., AND ENDICOTT, E. T., *Gastroenterology*, **9**, 718–35 (1947)
51. TIDWELL, H. C., SLESINSKI, F. A., AND TREADWELL, C. R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 482–85 (1947)
52. HOMBURGER, F., *Am. J. Med. Sci.*, **212**, 68–75 (1946)
53. WHEELER, J. E., AND GYÖRGY, P., *Am. J. Med. Sci.*, **215**, 267–72 (1948)
54. KINSELL, L. W., HARPER, H. A., BARTON, H. C., MICHAELS, G. D., AND WEISS, H. A., *Science*, **106**, 589–90 (1947)
55. HARPER, H. A., AND UKEYAMA, K., *Proc. Soc. Exptl. Biol. Med.*, **68**, 296–300 (1948)
56. JOHNSON, R. M., DEUEL, H. J., JR., MOREHOUSE, M. G., AND MEHL, J. W., *J. Nutrition*, **33**, 371–88 (1947)
57. COX, W. M., JR., MUELLER, A. J., ELMAN, R., ALBANESE, A. A., KEMMERR, K. S., BARTON, R. W., AND HOLT, L. E., JR., *J. Nutrition*, **33**, 437–57 (1947)
58. RIEGEL, C., KOOP, C. E., AND GRIGGER, R. P., *Proc. Soc. Exptl. Biol. Med.*, **62**, 7–8 (1946)
59. KIMBALL, S., AND CHAPPLE, W. A. C., *Gastroenterology*, **8**, 185–90 (1947)
60. PATEK, A. J., JR., *J. Mt. Sinai Hosp. N. Y.*, **14**, 1–8 (1947)
61. WADE, L., *J. Lab. Clin. Med.*, **32**, 1522–23 (1947)
62. FREEMAN, S., *Ann. Rev. Physiol.*, **8**, 169–98 (1946)
63. LABBY, D. H., SHANK, R. E., KUNKEL, H. G., AND HOAGLUND, C. L., *J. Am. Med. Assoc.*, **133**, 1181–90 (1947)
64. CASALS, J., AND OLITSKY, P. K., *Proc. Soc. Exptl. Biol. Med.*, **63**, 383–90 (1946)
65. SVIRBELY, J. L., MONACO, A. R., AND ALFORD, W. C., *J. Lab. Clin. Med.*, **31**, 1133–43 (1946)
66. LI, T.-W., AND FREEMAN, S., *Am. J. Physiol.*, **145**, 158–65 (1945)
67. LI, T.-W., AND FREEMAN, S., *Am. J. Physiol.*, **148**, 358–64 (1947)
68. LI, T.-W., FREEMAN, S., HOUGH, V. H., AND GUNN, F. D., *Am. J. Physiol.*, **145**, 166–76 (1945)

69. Ashworth, C. T., and Mason, M. F., *Am. J. Path.*, **22,** 369–77 (1946)
70. Ashworth, C. T., *Proc. Soc. Exptl. Biol. Med.*, **66,** 382–85 (1947)
71. Jolliffe, N., and Jellinek, E. M., *Quart. J. Studies Alc.*, **2,** 544–83 (1941)
72. Rogers, W. N., *Quart. J. Studies Alc.*, **7,** 325–40 (1946)
73. Rosin, A., and Doljanski, L., *Am. J. Path.*, **22,** 317–35 (1946)
74. Rosin, A., and Doljanski, L., *Proc. Soc. Exptl. Biol. Med.*, **62,** 62–64 (1946)
75. Williams, W. L., and Frantz, M., *Anat. Record.*, **100,** 547–60 (1948)
76. Glynn, L. E., and Himsworth, H. P., *Clin. Sci.*, **6,** 235–41 (1948)
77. McCord, C. P., Sterner, J. H., Kline, L. L., and Williams, P. E., *Occupational Med.*, **1,** 160–67 (1946)
78. Brieger, H., and Friedman, M. H. F., *Occupational Med.*, **2,** 463–69 (1946)
79. Brunschwig, A., Johnson, C., and Nichols, S., *Proc. Soc. Exptl. Biol. Med.*, **60,** 388–91 (1945)
80. György, P., Seifert, J., Tomarelli, R. M., and Goldblatt, H., *J. Exptl. Med.*, **83,** 449–62 (1946)
81. Bollman, J. L., *Trans. Conf. Liver Injury, 5th Conf.*, 11–15 (Josiah Macy, Jr. Foundation, N. Y., Sept. 26–27, 1946)
82. Hoffbauer, F. W., *Trans. Conf. Liver Injury, 5th Conf.*, 21–30 (Josiah Macy, Jr. Foundation, N. Y., Sept. 26–27, 1946)
83. Bénard, H., Gajdos-Torok, M., and Gajdos, A., *Compt. rend. soc. biol.*, **141,** 122–23 (1947)
84. Shaffer, C. B., Carpenter, C. P., and Moses, C., *J. Ind. Hyg. Toxicol.*, **28,** 87–94 (1946)
85. Drill, V. A., and Loomis, T. A., *J. Pharmacol. Exptl. Therap.*, **90,** 138–49 (1947)
86. Sellers, E. A., Lucas, C. C., and Best, C. H., *Brit. Med. J.*, **I,** 1061–65 (1948)
87. Steinberg, B., and Martin, R. A., *Arch. Path.*, **41,** 1–10 (1946)
88. Morrione, T. G., *J. Exptl. Med.*, **85,** 217–25 (1947)
89. Warren, S., and Wahi, P. N., *Arch. Path.*, **44,** 563–70 (1947)
90. Bondy, P. K., Sheldon, W. H., and Evans, L., *Federation Proc.*, **7,** 10 (1948)
91. Hueper, W. C., *Medicine*, **27,** 43–103 (1948)
92. Baxter, J. H., *J. Pharmacol. Exptl. Therap.*, **91,** 345–49 (1947)
93. Baxter, J. H., and Mason, M. F., *J. Pharmacol. Exptl. Therap.*, **91,** 350–56 (1947)
94. Baxter, J. H., *Am. J. Path.*, **24,** 503–25 (1948)
95. Rubarth, S., *Acta Path. Microbiol. Scand.*, Suppl. 69, 1–222 (1947)
96. Witts, L. J., *Brit. Med. J.*, **I,** 1–4 (1947)
97. Glynn, L. E., *Nutrition Abstracts & Revs.*, **16,** 751–62 (1947)
98. Rao, R., *Nature*, **161,** 446–47 (1948)
99. Best, C. H., Lucas, C. C., Patterson, J. M., and Ridout, J. H., *Biochem. J.*, **40,** 368–73 (1946)
100. Ridout, J. H., Lucas, C. C., Patterson, J. M., and Best, C. H., *Biochem. J.*, **40,** 494–99 (1946)
101. Best, C. H., Lucas, C. C., Patterson, J. M., and Ridout, J. H., *Science*, **103,** 12–13 (1946)
102. Best, C. H., *Am. J. Digestive Diseases*, **13,** 155–59 (1946)

103. MONTGOMERY, M. L., ENTENMAN, C. AND CHAIKOFF, I. L., *Am. J. Physiol.*, **148,** 239–42 (1947)
104. CHAIKOFF, I. L., ENTENMAN, C., AND MONTGOMERY, M. L., *J. Biol. Chem.*, **168,** 177–81 (1947)
105. ENTENMAN, C., CHAIKOFF, I. L., AND REICHERT, F. L., *Endocrinology,* **42,** 210–14 (1948)
106. ENTENMAN, C., CHAIKOFF, I. L., GILLMAN, T., AND REICHERT, F. L., *Endocrinology,* **42,** 215–22 (1948)
107. CLARK, D. E., EILERT, M. L., AND DRAGSTEDT, L. R., *Am. J. Physiol.*, **144,** 620–25 (1945)
108. EILERT, M. L., AND DRAGSTEDT, L. R., *Am. J. Physiol.*, **147,** 346–51 (1946)
109. CANEPA, J. F., AND IVY, A. C., *Federation Proc.*, **7,** 17 (1948)
110. LI, T.-W., AND FREEMAN, S., *Am. J. Physiol.*, **145,** 646–59, 660–65, 667–75 (1946)
111. GROEN, J., *Science,* **107,** 425–26 (1948)
112. CAMPBELL, J., *Am. J. Physiol.*, **147,** 742–47 (1946)
113. MILLER, L. L., ROGERS, C. A., LAMSON, B. G., AND LAMBIE, M. W., *Am. J. Med. Sci.*, **214,** 84–88 (1947)
114. DRILL, V. A., AND LOOMIS, T. A., *Proc. Soc. Exptl. Biol. Med.*, **61,** 374–76 (1946)
115. RICH, A. R., BERTHRONG, M., AND GERMUTH, F. G., JR., *Trans. Assoc. Am. Physicians* (In press)
116. WILSON, J. W., AND LEDUC, E. H., *Anat. Record,* **97,** 471–93 (1947)
117. KOSTERLITZ, H. W., *J. Physiol. (London),* **106,** 194–210 (1947)
118. HARRISON, H. C., AND LONG, C. N. H., *J. Biol. Chem.*, **161,** 545–57 (1945)
119. ROSE, C. S., MACHELLA, T. E., AND GYÖRGY, P., *Proc. Soc. Exptl. Biol. Med.*, **64,** 352–54 (1947); **67,** 198–99 (1948)
120. SCHWARZ, K., *Z. physiol. Chemie,* **281,** 101–8, 109–16 (1944)
121. NEUBERGER, A., AND WEBSTER, T. A., *Biochem. J.*, **41,** 449–57 (1947)
122. GLYNN, L. E., HIMSWORTH, H. P., AND NEUBERGER, A., *Brit. J. Expertl. Path.*, **26,** 326–37 (1945)
123. REINHARDT, W. O., AND BAZELL, A. H., *Proc. Soc. Exptl. Biol. Med.*, **62,** 270–71 (1946)
124. MUNRO, F. L., HART, E. R., MUNRO, M. P., AND WALKING, A. A., *Am. J. Physiol.*, **145,** 206–10 (1945)
125. MUNRO, M. P., AND AVERY, A., *Am. J. Physiol.*, **146,** 673–76 (1946)
126. OPPENHEIMER, M. J., AND FLOCK, E. V., *Am. J. Physiol.*, **149,** 418–22 (1947)
127. DRABKIN, D. L., *J. Biol. Chem.*, **171,** 395–408, 409–17 (1947)
128. VARS, H. M., AND GURD, F. N., *Am. J. Physiol.*, **151,** 391–98, 399–404 (1947)
129. GURD, F. N., VARS, H. M., AND RAVDIN, I. S., *Am. J. Physiol.*, **152,** 11–21 (1948)
130. DRABKIN, D. L., *Federation Proc.*, **7,** 151–52 (1948)
131. DENTON, R. W., AND IVY, A. C., *Am. J. Physiol.*, **152,** 460–64 (1948)
132. NEWMAN, E. A., AND GROSSMAN, M. I., *Federation Proc.*, **7,** 85 (1948)
133. VARS, H. M., AND FRIEDGOOD, C. E., *Federation Proc.*, **7,** 196 (1948)
134. RITTENBERG, R., SPROUL, E. E., AND SHEMIN, D., *Federation Proc.*, **7,** 180 (1948)
135. WACHSTEIN, M., *Arch. Path.*, **40,** 57–67 (1945)

136. WACHSTEIN, M., AND ZAK, F. G., *Arch. Path.*, **42**, 501–16 (1946)
137. WACHSTEIN, M., AND ZAK, F. G., *Proc. Soc. Exptl. Biol. Med.*, **62**, 73–76 (1946)
138. SHERLOCK, S., AND WALSHE, V., *J. Path. Bact.*, **59**, 615–30 (1947)
139. DEANE, H. W., *Am. J. Anat.*, **80**, 321–59 (1947)
140. JACOBY, F., *J. Physiol. (London)*, **106**, 33P (1947)
141. JALLING, O., LAURSEN, T., AND VOLOVARTZ, K., *Acta Physiol. Scand.*, **10**, 70–77 (1945)
142. HOFFMEYER, J., JALLING, O., AND SCHØNHEYDER, F., *Acta Physiol. Scand.*, **11**, 160–67 (1946)
143. GAD, I., *Acta Physiol. Scand.*, **11**, 151–59 (1946)
144. DALGARD, J. B., *Acta Physiol. Scand.*, **13**, 310–21 (1947)
145. FLOCK, E. V., AND BOLLMAN, J. L., *Federation Proc.*, **7**, 154–55 (1948)
146. ALSTAD, G., *Am. J. Med. Sci.*, **213**, 257–67 (1947)
147. JERSILD, M., *New Engl. J. Med.*, **237**, 8–12 (1947)
148. BEAN, W. B., *Medicine*, **24**, 243–331 (1945)
149. LLOYD, C. W., AND WILLIAMS, R. H., *Am. J. Med.*, **4**, 315–30 (1948)
150. RATHER, L. J., *Arch. Internal Med.*, **80**, 397–402 (1947)
151. FEINER, M., KRICHESKY, B., AND GLASS, S. J., *Proc. Soc. Exptl. Biol. Med.* **66**, 235–39 (1947)
152. KLATSKIN, G., SALTER, W. T., AND HUMM, F. D., *Am. J. Med. Sci.*, **213**, 19–30 (1947)
153. SALTER, W. T., KLATSKIN, G., AND HUMM, F. D., *Am. J. Med. Sci.*, **213**, 31–36 (1947)
154. HIBBS, R. E., *Am. J. Med. Sci.*, **213**, 176–77 (1947)
155. JACOBS, E. C., *Ann. Internal Med.*, **28**, 792–97 (1948)
156. GILDER, H., AND HOAGLUND, C. L., *Proc. Soc. Exptl. Biol. Med.*, **61**, 62–65 (1946)
157. ZONDEK, B., AND BLACK, R., *J. Clin. Endocrinol.*, **7**, 519–29 (1947)
158. HOOKER, C. W., DRILL, V. A., AND PFEIFFER, C. A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 192–94 (1947)
159. EMERY, F. E., AND JOYCE, H. E., *J. Endocrinol.*, **4**, 371–74 (1946)
160. SEGALOFF, A., *Endocrinology*, **38**, 212–14 (1946)
161. ROBERTS, S., AND SZEGO, C. M., *Endocrinology*, **40**, 73–85 (1947)
162. GYÖRGY, P., *Proc. Soc. Exptl. Biol. Med.*, **60**, 344–49 (1945)
163. ZONDEK, B., AND FINKELSTEIN, M., *Science*, **105**, 259–60 (1947)
164. DRILL, V. A., AND PFEIFFER, C. A., *Endocrinology*, **38**, 300–7 (1946)
165. GYÖRGY, P., ROSE, C. S., AND SHIPLEY, R. A., *Arch. Biochem.*, **12**, 125–33 (1947)
166. PICK, E. P., *J. Mt. Sinai Hosp., N. Y.*, **13**, 167–76 (1946)
167. LABBY, D. H., AND HOAGLUND, C. L., *Proc. Soc. Exptl. Biol. Med.*, **63**, 110–14 (1946)
168. LABBY, D. H., AND HOAGLUND, C. L., *J. Clin. Invest.*, **26**, 343–53 (1947)
169. PERERA, G. A., *Ann. Internal Med.*, **24**, 643–47 (1946)
170. LAYNE, J. A., AND SCHEMM, F. R., *Gastroenterology*, **9**, 705–17 (1947)
171. RALLI, E. P., ROBSON, J. S., CLARKE, D., AND HOAGLUND, C. L., *J. Clin. Invest.*, **24**, 316–25 (1945)
172. LESLIE, S. H., AND RALLI, E. P., *Endocrinology*, **41**, 1–11 (1947)

173. DRILL, V. A., AND FRAME, B., *Federation Proc.*, **7**, 215–16 (1948)
174. BAEZ, S., MAZUR, A., AND SHORR, E., *Federation Proc.*, **7**, 5 (1948)
175. HIGGINS, G., KELSALL, A. R., O'BRIEN, J. R. P., STEWART, A. M., AND WITTS, L. J., *Quart. J. Med.*, **16**, 263–73 (1947)
176. CROSBY, R. C., AND COONEY, E. A., *New Engl. J. Med.*, **235**, 581–85 (1946)
177. LANE, J. D., *Military Surgeon*, **102**, 177–78 (1948)
178. THORN, G. W., ARMSTRONG, S. H., JR., AND DAVENPORT, V. D., *J. Clin. Invest.*, **25**, 304–23 (1946)
179. PATEK, A. J., JR., MANKIN, H., COLCHER, H., LOWELL, A., AND EARLE, D. D., JR., *J. Clin. Invest.*, **27**, 135–44 (1948)
180. MANKIN, H., AND LOWELL, A., *J. Clin. Invest.*, **27**, 145–53 (1948)
181. KUNKEL, H. G., LABBY, D. H., AHRENS, E. H., JR., SHANK, R. E., AND HOAGLUND, C. L., *J. Clin. Invest.*, **27**, 305–19 (1948)
182. ARMSTRONG, S. H., *Am. J. Med.*, **4**, 390–97 (1948)
183. BOLTON, C., AND BARNARD, W. G., *J. Path. Bact.*, **34**, 701–9 (1931)
184. GRINDLAY, J. H., CAIN, J. C., BOLLMAN, J. L., FLOCK, E. V., AND MANN, F. C., *Federation Proc.*, **6**, 117 (1947)
185. CAIN, J. C., GRINDLAY, J. H., BOLLMAN, J. L., FLOCK, E. V., AND MANN, F. C., *Surg. Gynecol. Obstet.*, **85**, 559–62 (1947)
186. GRINDLAY, J. H., FLOCK, E. V., AND BOLLMAN, J. L., *Federation Proc.*, **7**, 45 (1948)
187. KNISELY, M. H., BLOCH, E. H., AND WARNER, L., *Trans. Conf. Liver Injury, 4th Conf.*, 21–41 (Josiah Macy, Jr. Foundation, N. Y., Oct. 24–26, 1945)
188. PRINZMETAL, M., ORNITZ, E. M., JR., SIMKIN, B., AND BERGMAN, H. C., *Am. J. Physiol.*, **152**, 48–52 (1948)
189. SHERLOCK, S., AND WALSHE, V., *Clin. Sci.*, **118**, 113–23 (1946)
190. WHIPPLE, A. O., *Bull. N. Y. Acad. Med.*, **22**, 251–53 (1946)
191. BLAKEMORE, A. H., *Surg. Gynecol. Obstet.*, **84**, 645–53 (1947)
192. BLALOCK, A., *Ann. Surg.*, **125**, 129–41 (1947)
193. LINTON, R. R., JONES, C. M., AND VOLWILER, W., *Surgical Clin. North Am.*, **27**, 1162–70 (1947)
194. WANGENSTEEN, O. H., *Can. Med. Assoc. J.*, **53**, 309–31 (1945)
195. PHEMISTER, D. B., AND HUMPHREYS, E. M., *Ann. Surg.*, **126**, 397–410 (1947)
196. HOFFBAUER, F. W., BOLLMAN, J. L., AND GRINDLAY, J. H., *J. Lab. Clin. Med.*, **32**, 1401 (1948)
197. KERSHNER, D., HOOTON, T. C., AND SHEARER, E. M., *Arch. Surg.*, **53**, 425–34 (1946)
198. SCHAFER, P. W., AND KOZY, J. S., *Surgery*, **22**, 959–64 (1947)
199. BOLLMAN, J. L., *Trans. Conf. Liver Injury, 7th Conf.*, 21–26 (Josiah Macy, Jr. Foundation, N. Y., Jan. 14–15, 1948)
200. DRILL, V. A., *Federation Proc.*, **7**, 215 (1948)
201. WIGGERS, C. J., OPDYKE, D. F., AND JOHNSON, J. R., *Am. J. Physiol.*, **146**, 192–206 (1946)
202. WILHELMI, A. E., *Ann. Rev. Physiol.*, **10**, 259–76 (1947)
203. SELKURT, E. E., ALEXANDER, R. S., AND PATTERSON, M. B., *Am. J. Physiol.*, **149**, 732–42 (1947)
204. FINE, J., SELIGMAN, A. M., AND FRANK, H. A., *Ann. Surg.*, **126**, 1002–9 (1947)

205. SHORR, E., *Am. J. Med.*, **4**, 120–29 (1948)
206. REINHARD, J. J., GLASSER, O., AND PAGE, I. H., *Federation Proc.*, **7**, 98–99 (1948)
207. SHORR, E., AND ZWEIFACH, B. W., *Federation Proc.*, **7**, 115 (1948)
208. BRADLEY, S. E., *Bull. New Engl. Med. Center*, **7**, 224–28 (1945)
209. BRADLEY, S. E., INGELFINGER, F. J., BRADLEY, G. P., AND CURRY, J. J., *J. Clin. Invest.*, **24**, 890–97 (1945)
210. MUNNELL, E. W., AND TAYLOR, H. C., JR., *J. Clin. Invest.*, **26**, 952–56 (1947)
211. BRADLEY, S. E., INGELFINGER, F. J., GROFF, A. E., AND BRADLEY, G. P., *Proc. Soc. Exptl. Biol. Med.*, **67**, 206–7 (1948)
212. BRADLEY, S. E., *Trans. Conf. Liver Injury, 7th Conf.*, 53–56 (Josiah Macy, Jr., Foundation, N. Y., Jan. 14–15, 1948)
213. MYERS, J. D., *J. Clin. Invest.*, **26**, 1130–37 (1947)
214. LIPSCOMB, A., AND CRANDALL, L. A. JR., *Am. J. Physiol.*, **148**, 302–11 (1947)
215. COHN, C., LEVINE, R., AND STREICHER, D., *Am. J. Physiol.*, **150**, 299–303 (1947)
216. MASON, M. F., HAWLEY, G., AND SMITH, A., *Am. J. Physiol.*, **152**, 42–47 (1948)
217. WATSON, C. J., *Blood*, **1**, 99–120 (1946)
218. NEEFE, J. R., AND REINHOLD, J. G., *Gastroenterology*, **7**, 393–413 (1946)
219. WITH, T. K., *Acta Med. Scand.*, **123**, 166–180 (1946)
220. WITH, T. K., *Acta Med. Scand.*, **128**, 25–41 (1947)
221. ENACHESCO, M., COMANESCO, V., AND ZAMFIRESCO, M., *Acta Med. Scand.*, **126**, 205–23 (1946)
222. WITH, T. K., *Acta Med. Scand.*, **122**, 501–12 (1945)
223. LUPS, S., AND MEIJER, F. G. D., *Acta Med. Scand.*, **126**, 85–96 (1946)
224. WITH, T. K., *Acta Physiol. Scand.*, **10**, 172–80, 181–92 (1945)
225. GRAY, C. H., *Quart. J. Med.*, **16**, 135–42 (1947)
226. GRAY, C. H., AND WHIDBORNE, J., *Biochem. J.*, **41**, 155–61 (1947)
227. MARTIN, N. H., *Biochem. J.*, **42**, XV (1948)
228. LOEWY, A., AND FREEMAN, L. W., *Am. J. Physiol.*, **152**, 205–9 (1948)
229. WITH, T. K., *Acta. Med. Scand.*, **125**, 588–99 (1946)
230. BIERING-SØRENSEN, K., AND WITH, T. K., *Acta Paediatr.*, **34**, 63–71 (1947)
231. WATSON, C. J., AND HAWKINSON, V., *Am. J. Clin. Path.*, **17**, 108–15 (1947)
232. PELLEGRINO, E., PATEK, A. J., JR., COLCHER, A., AND DOMANSKI, B., *J. Lab. Clin. Med.*, **32**, 397–402 (1947)
233. NAUMANN, H. N., *J. Lab. Clin. Med.*, **32**, 1503–7 (1947)
234. WATSON, C. J., AND LARSON, E. A., *Physiol. Revs.*, **27**, 478–510 (1947)
235. DENT, C. E., AND RIMINGTON, C., *Biochem. J.*, **41**, 253–60 (1947)
236. LONDON, I. M., WEST, R., SHEMIN, D., AND RITTENBERG, D., *Federation Proc.*, **7**, 169 (1948)
237. SCOTT, C. C., *Am. J. Physiol.*, **144**, 626–31 (1945)
238. BOYD, E. M., EARL, J. T., JACKSON, S., PALMER, B., AND STEVENS, M., *Am. J. Physiol.*, **145**, 186–89 (1945)
239. IRVIN, J. L., JOHNSTON, C. G., AND SHARP, E. A., *Am. J. Physiol.*, **146**, 293–306 (1946)
240. JOHNSTON, C. G., AND IRVIN, J. L., *J. Clin. Invest.*, **26**, 802–14 (1947)

241. With, T. K., *Acta Med. Scand.*, **122,** 513–28 (1945)
242. Snape, W. J., Wirts, C. W., and Cantarow, A., *Proc. Soc. Biol. Med.*, **66,** 468–70 (1947)
243. Grafflin, A. L., *Am. J. Anat.*, **81,** 63–116 (1947)
244. Miller, A. T., Jr., *Am. J. Physiol.*, **151,** 229–33 (1947)
245. Mixer, H. W., Rigler, L. G., and Gonzalez-Oddone, M. V., *Gastroenterology*, **9,** 64–80 (1947)
246. Halpert, B., Russo, P. E., and Cushing, V. D., *Proc. Soc. Biol. Med.*, **63,** 102–4 (1946)

DIGESTIVE SYSTEM[1]

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Appetite, Hunger, and Thirst

Appetite and hunger.—Experiments reported by Goetzl & Stone (1), if they can be confirmed, may provide a quantitative method for the study of human appetite. These authors devised a means of measuring olfactory acuity with a high degree of reproducibility and found that the acuity of this sense increased progressively toward meal time and declined again after food was taken. In a second paper (2) they report that amphetamine sulfate causes a parallel decrease in olfactory acuity and appetite. The suggested possibility that foods owe their satiety value to an amphetamine-like component seems somewhat remote.

In experiments on mice allowed free selection of foods Donhoffer & Vonotzky (3) report that the animals increased their voluntary intake of food, chiefly the carbohydrates, when exposed to low temperature (10°to 11°C.) or when given thyroxine (4). At high temperatures (29°to33°C.) the food intake decreased and again carbohydrate was preferred. Work by Dugal, Leblond & Thérien (271) has shown that rats select a high fat, high protein diet at low temperatures (0°to 20°C.). Scott & Verney (5) found that rats allowed free selection of food avoided lactose, which causes diarrhea and retards growth in these animals. As a result of another similar study these authors (6) conclude that selection of foods containing vitamins of the B complex by vitamin-deficient rats is a result of previous favorable experience with such foods rather than a "true hunger."

Recent evidence indicates that rats may voluntarily limit their carbohydrate intake to the amount they can metabolize. Lundbaek & Stevenson (7) found that rats made obese by hypothalamic lesions when put on a carbohydrate diet decreased their food intake after a time. Normal or obese animals that were shifted from fat to carbohydrate showed a decrease in food intake more marked

[1] This review covers the period from June, 1947 to June, 1948.

in the obese animals. Vartiainen & Bastman-Heiskanen (8) found that rats made diabetic with alloxan and allowed free selection of food decreased their glucose intake. Soulairac (9) believes that the appetite for sugar in rats is determined by its initial absorption and that this in turn is influenced by the endocrine glands. In experiments by Hanson & Grossman (10) the appetite of dogs was not significantly affected by intravenous injection of 200 to 400 cc. of 20 per cent glucose in 0.3 per cent sodium chloride or by sodium chloride alone.

The inability of nonnutritive materials to satisfy appetite (or appease hunger) was demonstrated in experiences related by Hoelzel (11), who in his youth tried eating sand, cotton-wool, cellulose, glass beads, etc., in an effort to reduce what he conceived to be an abnormal craving for food. He remarks that after eating twelve ounces of glass beads he was hungrier than before. Somewhat similar conclusions can be drawn from the experiments of Adolph (12), who tried the effect on voluntary food intake of rats of diluting the food with kaolin, cellulose-flour, or water. The animals continued to ingest their normal caloric requirements until the dilutions were so great that this became impractical.

On the basis of the greater length of the large intestine and the shorter small intestine and fewer Peyer's patches in wild Alexandrine rats as compared to wild and domestic Norway rats, Richter & Hall (13) conclude that the Alexandrine rat is primarily herbivorous and the Norway rat carnivorous.

Several observations indicate that there is a central mechanism for appetite which is not dependent on sensory stimuli from the stomach and intestine. Ginsberg, Feldman & Necheles (14) found that unpleasant odors which abolished appetite in human subjects did not inhibit gastric hunger contractions in humans and did so only occasionally in dogs. MacDonald & associates (15) have reported a normal desire for food in patients following total gastrectomy. Harris, Ivy & Searle (16) noted that the desire for food could be abolished over long periods of time, up to twenty-eight days, by giving injections of amphetamine near meal time in vagotomized-sympathectomizied dogs as well as in normal controls.

Thirst.—The obscure mechanism of thirst was further confused by the experiments of Holmes & Gregersen (17), who found that 250 to 300 cc. of 5 per cent saline intravenously decreased salivary secretion and caused intense thirst in patients but not if the sub-

jects were given 400 to 600 cc. of water to drink twenty to thirty minutes before the injection, although the blood changes were identical. Isotonic saline (300 cc. intravenously) failed to influence salivary secretion or to cause thirst.

Salivary Glands and Saliva

Citric acid solution or water sprayed into the mouth as well as pilocarpine subcutaneously increases salivary secretion in man according to Kliorin (18). Pilocarpine is the most effective, water the least. Optimum concentration of citric acid was 0.75 per cent. In experiments by Koropov (19) salivary secretion was diminished in dogs infected with staphylococci, but the infection had less inhibiting effect if the superior cervical ganglion was removed.

Yonkman (20) reports that pyribenzamine potentiates the action of epinephrine and of sympathetic stimulation on salivary secretion in the cat and on the small intestine in dogs. This is explained by the suggestion that histamine detoxicates epinephrine and this effect is opposed by the antihistaminic compounds.

Citric acid in concentrations of 0.5 to 2.0 mg. per cent was found in human saliva by Zipkin (21); its presence in these high concentrations is believed to be a factor in dental caries. Thiocyanate appears in the saliva in greater concentrations than in the serum according to the Fischmanns (22). The output is increased by smoking.

Lura (23) studied phosphates and phosphatase activity in human saliva and salivary glands. Greatest phosphatase activity was in submaxillary tissue; the optimum pH for the enzyme was 5.5. A proteinase is present in mouse saliva, active at pH 8.0, according to Junqueira, Rabinovitch & Fajer (24). These authors also report that zymogen granules appear in the submaxillary gland of male mice at an earlier age, by sixteen to twenty-five days, than in female mice. In the male the gland contains more granules and produces more enzymes throughout life.

The salivary glands participate in the "alarm reaction" (Selye), according to Ehrich & Seifter (25), in that after large doses of various toxic chemical agents there was loss of zymogen granules and, in some instances, focal necrosis in these glands. Krasnovskaya & Efimov (26) find that a substance toxic for frog muscle appears in human saliva at elevations of four thousand meters and higher.

Esophagus

Stewart (27) found the velocity of test objects carried by frog ciliated epithelium to be constant as long as the weight per unit area was constant. The rate of transport of the test object was increased by stroking the adjacent epithelium.

In so-called cardiospasm Templeton (28) found peristalsis weak in the lower esophagus; the inhibitory phase of the peristaltic wave fails to reach the sphincter to produce relaxation. The condition probably involves failure of the myenteric plexus.

The pharyngoesophageal nerve was found by Hwang (29) to be the efferent pathway for primary and secondary peristalsis of the cervical esophagus. Section of the recurrent laryngeal nerves close to the cricoid cartilage abolishes generally the swallowing reflex and secondary peristalsis of the cervical esophagus but not the primary peristalsis.

From measurement of intralumenal pressures in the lower esophagus and fundus in man, Brody, Lawson & Quigley (30) concluded that the wave of inhibition preceding the wave of contraction may be a reserve mechanism brought into play when the contraction wave alone is inadequate to propel a bolus.

Hwang & Unna (31) found in dogs under pentobarbital that curare paralyzed skeletal muscle and both the cervical and thoracic portions of the esophagus earlier than the diaphragm. The esophagus took four or five times longer to recover than the diaphragm.

Gastric Motility

Brody & Quigley (32) have devised an elegant method for recording intragastric and intraduodenal pressures in the human by means of open tubes in the stomach and duodenum leading to optical manometers. In the stomach, phasic pressure changes occur as simple, monophasic waves produced by antral peristalsis. In the duodenum, pressure waves are multiphasic indicating progression of rhythmic contractions. A rolling type of pressure wave corresponding to Cole's "systole" occurs in the body of the empty stomach.

Two studies on the effect of fat on the rate of gastric emptying in man appear to have given conflicting results. Henschel, Keys & associates (33) using a small test meal (about 200 kcal.) found that replacing other ingredients with fat up to 70 per cent of total cal-

ories did not significantly alter gastric emptying time. Carbohydrate up to 85 per cent was also without effect but 55 per cent protein slightly delayed emptying. Annegers & Ivy (34, 35) using a more substantial meal (1500 kcal.) found that all but a few of their subjects showed significant delay in emptying when the fat content of the meal was increased from 6 per cent to 8 per cent and likewise when it was increased from 8 per cent to 14 per cent. The conflict in results may be attributed to differences in the total quantities of fat involved. The heavy use of fats in the Mexican cuisine was considered by Nimeh (36) to be a factor along with anoxia due to altitude in the retarded gastric emptying which he observed in Mexico City in permanent residents as well as in tourists. Véghelyi (37) finds gastric lipase always present in the normal stomach. He suggests that delayed gastric emptying may occur as a result of decreased digestion of fat due to diminished gastric lipase. This surprising speculation appears to be without much basis in fact.

Northup & Van Liere (38) found a significant increase in the rate of gastric emptying after giving pentobarbital to human subjects, but no change with chloral hydrate, bromural, or paraldehyde. According to Shapiro & Ivy (39) carbonation does not alter the rate of gastric emptying of a 10 per cent sucrose solution as judged by the rise in blood sugar during absorption. Jefferson & Necheles (40) observed acceleration of gastric emptying after left-sided phrenicotomy.

The observation by Quigley and his associates (272) that after vagotomy insulin hypoglycemia causes inhibition of gastric tone and motility in dogs was again confirmed by Feldman & Morrison (41). Efforts to duplicate these results in two vagotomized patients failed. Patterson & Scantlebury (42) found that distention of the lungs in the bullfrog caused inhibition of gastric motility. Brody & Quigley (43) measured the decrease in intragastric pressure following administration of nitroglycerine or amyl nitrite and found it varied from 3.0 to 7.3 cm. of water.

Singh & Singh (44) have studied the behavior of the stomach muscle of the frog under aerobic and anaerobic conditions and report significant differences. The muscle may maintain considerable tension for several hours in the absence of oxygen and finally die in a contracted state.

Swenson & Manges (45) have reviewed the roentgen findings in functional disturbances of the gastrointestinal tract and have

attempted to interpret their findings in terms of the physiology of the organs and the autonomic nerves.

Gastric Secretion

An attempt to clarify the site of formation of hydrochloric acid by the gastric mucosa was made by Bradford & Davies (46). By means of acid-base indicators they found in the isolated frog and polecat stomach mucosa that the deeper regions of the mucosa and the cytoplasm of the parietal cells were alkaline (pH 7.2 to 7.6) during acid secretion while the canaliculi, the secretory surface, and the lumen of some of the tubules were acid (often below pH 4.8 and pH 1.4, depending on the dye used). At no time were all the parietal cells secreting actively. The theory of Visscher (273) that dyes pass through the cell membrane in undissociated form was not found to hold in these experiments, since unionized phenolphthalein was not secreted while ionized acriflavine was.

The oxidative metabolism of the mouse whole stomach was investigated by Davenport (47) and the data then calculated for the mucosal metabolism. The oxygen uptake was large and was not affected by the addition of glucose, lactose, or pyruvate, but was depressed by fructose. Cyanide, iodoacetate, arsenate, and fluoride decreased oxygen consumption; on the other hand, histamine increased it slightly, while thiocyanate, urogastrone, and enterogastrone were without significant effect. The stomach produced and oxidized lactic and pyruvic acids, and reduced pyruvic to lactic acid. Acetaldehyde was not formed from pyruvic acid, hence the theory of Bull & Gray (274) that pyruvic acid is the precursor of hydrochloric acid is not tenable. A finding of interest was the formation of large amounts of lactic acid from pyruvic acid even when oxidation of pyruvic acid was inhibited.

An interesting experiment by Davies & Terner (48) on isolated frog and toad gastric mucosa throws some light on the secretion of water. Measurements of rates of water secretion and of respiration were made. Under anaerobic conditions, no secretion of water or acid was observed but small amounts of a neutral liquid traversed the mucous membrane either way, depending on the direction of applied hydrostatic pressure. However, under aerobic conditions both the secreting and nonsecreting mucosa resisted water transfer when moderate pressure was applied to either side of the membrane. The mucosa secreted against a pressure applied to the secretory surface. Thiocyanate did not affect the increase in oxygen uptake

which resulted from the introduction of histamine [cf. Davenport (47)] but strongly inhibited the rate of acid and, to some extent, water secretion. Davies & Terner (48) feel that the transport of water across the mucosal membrane is an active secretory process and question the conclusion of Davenport & Fisher (275) that the energy requirements for the movement of water are derived from differences in hydrostatic pressure between blood and gastric juice. The output of hydrochloric acid by the isolated frog gastric mucosa was calculated by Davies *et al.* (49) to be mole for mole many times greater than its oxygen uptake, which would invalidate the supposition that the hydrogen ion is derived from glucose.

Horstmann (50) found a constant linear relationship between total chloride and acid chloride in human insulin-provoked gastric secretion. Linde, Teorell & Öbrink (51) in anesthetized cats and Heidenhain pouch dogs obtained results by indirect means which according to them, indicate that the primary acidity of the gastric juice does not remain constant but increases from 170 to 350 m.eq. per l. with decreasing rates of secretion. By extrapolation, the acidity at the "lowest possible rate of secretion" would be as great as 464 m.eq. per l. (!). The authors state that they have sought in vain for a fallacy in this method; a further search seems advisable. Teorell (52) considers the variations in electrolyte concentration in mammalian gastric juice to be due to diffusion across the stomach mucosa which acts as a dialyzing membrane for hydrochloric acid and alkali chloride. Keller & Pisha (53) suggest that sodium chloride is decomposed in the stomach by "electrolysis" and that during secretion the parietal cell behaves as a negative center, drawing the positive sodium moleclue (not ion!) into the blood. A superficial resemblance of this to the "diffusion theory" of Teorell (52) is noticeable. Kurtz & Clark (54) measured carbon dioxide diffusion into the stomach lumen before and during stimulation of secretion with histamine. The reciprocal relationship between carbon dioxide diffusion and hydrochloric acid secretion was taken as presumptive evidence of the participation of carbon dioxide, bicarbonate, and carbonic anhydrase in the formation of hydrochloi ic acid. Hofstetter (55) reported confirmation of previous observations that the intragastric pH *in situ* was 1 to 2 units higher than the pH of the juice *in vitro*. Certain apparent discrepancies in previous observations on electric potential differences of the stomach in relation to gastric secretion are explained in a paper by Hokin & Rehm (56).

Schiff and collaborators (57) administered radioactive iodine intravenously in man and found the greatest concentration in the saliva, least in serum, and intermediate in the gastric juice. Selle & Miller (58) applied iodine 131 to the denuded unabraded skin of the pregnant rabbit and guinea pig near term and twelve to twenty-four hours later determined the radioiodine concentration in the fetuses delivered by laparotomy. Distribution in the fetus was similar to that in the mother. While the fetal thyroid took large amounts, over 90 per cent of the total fetal radioiodine was in the gastric contents. Less was found in the salivary gland than the stomach. Only low concentrations were found in the intestine and amniotic fluid, which would appear to exclude regurgitation and fetal swallowing as factors, unless subsequent concentration by the gastric epithelium was involved.

Forsgren (59) found in human subjects that the gastric acidity usually decreased during the day. Kowalewski (60) found the number of achlorhydrics to increase during 1941-1944 in a study among 1890 prisoners of war and probably is correct in attributing this to the semistarvation and low protein intake. Karp (61) reaffirms the views of Heidenhain and Pavlov that the fully innervated dog stomach does not secrete acid during the interdigestive phase in the absence of conditioned reflexes.

Babkin, Lawson & Karp (62, 63) describe the operation of gastroduodenoduodenostomy in the dog. The operation permits a "circus" movement of duodenal contents between duodenum and stomach, thus resulting in the presence within the fasting stomach of a fluid which is nearly always alkaline. The circulation of the gastric secretion through the duodenum stimulates the flow of bile and pancreatic juice which is passed into the stomach; transection of the pylorus to interrupt the "circus" movement again raises the intragastric acidity. Reed (64) found in nine patients with a subnormal gastric secretory response to an Ewald test meal that prefrontal lobotomy restored the secretion to normal levels.

Short-wave diathermy for three days was tried by Palmer (65) on ten normal subjects without any significant effects on gastric secretion being noted. This conflicts with the findings made on dogs in 1929 by Stewart & Boldyroff that diathermy increased all phases of gastric secretion. Bandes, Hollander & Bierman (66) found that induced hyperpyrexia resulted in temporary achlorhydria; the results however were not constant.

Ström & Uvnäs (67) compared in dogs with gastric fistula the

effect of various drugs on insulin-provoked gastric secretion. Methylscopalamine was slightly more effective than scopalamine and atropine in producing complete inhibition. Clark (68) compared the action of several drugs in the Cope gastric pouch dog and found atropine one thousand to three thousand times more effective than "trasentine," "syntropan," and "demerol." Grossman *et al.* (69) reported that a commercial preparation of "purified histaminase" inhibited the gastric secretory response of dogs with pouches to histamine, food, and parasympathomimetic drugs. Whether the depressant action was due to histaminase or to some other substance present in the tissue (kidney) extract is not known. The effects of rhythmic stimulation of the vagus nerves on the secretion of both acid and pepsin were found by Babkin & Karp (70) to be abolished by quinine and atabrine. Histamine-provoked secretion was not affected.

Block *et al.* (71) reported that the gastric secretion resulting from noxious emotional stimuli or insulin hypoglycemia, but not from the administration of liver extract, could be abolished in human subjects by atropine. In dogs with isolated vagally innervated and denervated pouches Merendino (72) found that morphine sulfate, dilaudid, and paregoric produced stimulation of acid gastric secretion. With development of general tolerance to morphine there developed also a decreased secretory response.

In ten patients with duodenal ulcer (73) and eleven patients with hypertension (74) the administration of tetraethylammonium chloride depressed fasting and test-meal gastric secretions. If the drug should prove to show no peripheral effect, the suppression of "fasting" secretion would suggest this secretion to be neurogenic in man.

Protein hydrolysate was found by Rossien (75) to be a short-acting antacid. Following the buffering effect there occurs stimulation of gastric secretion (76). In patients given histamine Littman & Grossman (77) found aluminum hydroxide gel to be superior to an equal amount of zirconuim phosphate as an antacid when the output of acid by the stomach was high. They call attention to a point often overlooked, namely, that proper evaluation of the efficiency of antacids must take into consideration the levels of acid output in control experiments.

Clark & Adams (78) determined the total twenty-four-hour volume and free acid output in the pouch secretion of two dogs with Cope pouches kept on a standard diet. Sodium bicar-

bonate and calcium carbonate, given by stomach tube, increased the volume and acid secretion while aluminum hydroxide gel and sodium citrate showed no significant effects. The absence of stimulation of secretion with the latter two substances suggests to these workers that the acid "rebound" secretion occurring with other alkalis is not due to removal of "acid inhibition." The problem of acid "rebound" following administration of sodium bicarbonate was also investigated by Hale & Grossman (79). Evidence is presented that "rebound" is not due to changes in systemic acid-base balance nor to gaseous distension or local effects.

Code *et al.* (80) determined the histamine content of gastric juice secreted by dogs with gastric pouches. The histamine-provoked secretion generally had detectable amounts of histamine, while mecholyl-stimulated secretion always, and insulin-stimulated secretion usually, had histamine. The amount of histamine activity in mecholyl juice bore no relation to the rate of hydrochloric acid secretion. The investigators did not interpret the results as proof against the view that histamine is essential for hydrochloric secretion but think rather that histamine may be a final common pathway for many gastric secretory stimuli. Campori (81) reported histamine present in the encapsulated masses which form in the rabbit's stomach after alfalfa feeding.

Hollander *et al.* (82) studied in dogs the characteristics of gastric pouch contents obtained following irritation by local application of mustard oil, clove oil, alcohol, etc. and by local massage. Certain agents elicited what may be considered a true mucus secretion but mustard oil evoked a transudate. Hollander & Lauber (83) concluded that the high pH values (up to pH 9.2) exhibited by the mucus secreted from the Heidenhain pouch after topical stimulation could in part be explained by loss of carbon dioxide. Their experiments suggest that the pH of gastric mucus at the moment of secretion from the mucous cell is approximately that of venous blood. Wolf & Wolff (84) studied the effect of direct application of numerous chemical agents to the gastric mucosa in a patient with a gastrostomy. Alcohol, clove oil, copper sulfate, and hydrochloric acid caused erythema and an opaque appearance. Presumably the opaque appearance was due to mucus.

The effect of local intra-arterial (gastrosplenic) injection of acetylcholine was the subject of a histophysiologic study by Morton & Stavraky (85). Following such administration only an

alkaline mucus was secreted. They concluded that the mucus was derived from the chief cells of the neck and possibly the surface epithelium.

Komarov *et al.* (86) reported that the secretion of mucin was independent of the secretion of acid and pepsin, indicating selective excitation of each type of secretory cell by a particular stimulus. Glass & Boyd (87, 88) described a colorimetric method for the quantitative determination of dissolved gastric mucin based on color reaction for tyrosine. Comparable results were obtained by Wolf & Wolff (84) by the methods of Glass & Boyd and of Komarov *et al.* (1947) when applied to mucin in gastric juice obtained by local irritation. Tulin, Gutmann & Almy (89) in twenty-nine "normal" and eighteen duodenal ulcer patients with active symptoms also found no difference in the mucin content of gastric juice secreted in response to a 14 per cent alcohol test meal. According to Gould & King (90) the effect of gastric mucin in augmenting the virulence of pathogenic bacetria is not due to the protective action of the viscous fluid in preventing access of the defensive mechanism of the host. They believe that gastric mucin contains a substance which is comparable with bacterial aggresins.

The Edwards' (91) described a procedure for studying gastric secretion *in vitro*. They found that nitrogen-containing compounds were necessary for the production of pepsin by isolated mucosa of the rat and rabbit.

Gastrin was prepared in two laboratories (92, 93) by different procedures. Both these procedures were developed originally for the preparation of secretin, a point which may indicate a similarity in chemical structure of the two gastrointestinal hormones. The effect of purified gastrin perparations could not be attributed to histamine (93). A method for the assay of gastrin and the requisite conditions for standardization were described (92).

Neither single nor continuous injections of a commercial preparation of enterogastrone [prepared and assayed as described by Greengard *et al.* (1946)] were found by Uvnäs (94) to inhibit histamine-stimulated gastric secretion in the cat. On the contrary, while the enterogastrone preparation did not excite gastric secretion, it did have a definite potentiating effect on histamine. Uvnäs thinks that the samples of "enterogastrone" he used may have been contaminated with gastrin. Such a possibility is likely in view of their rather similar chemical properties. A difference in species susceptibility may also be considered since the original assays were

done on dogs. In man with histamine- and insulin-provoked gastric secretion Kirsner *et al.* (95) found enterogastrone to yield inconsistent and negative results. The "enterogastrone" preparation used by these workers was apparently the same, or similar to, the one employed by Uvnäs (94) and the same comments apply.

The method of Friedman & Sandweiss (276) of using rats with pyloric ligation to study the ability of enterogastrone to inhibit gastric secretion was employed by Visscher (96) and Katz and coworkers (97). Electrophoretic separation of enterogastrone at pH 7.5 yielded seven fractions (97); according to Öbrink (98), purified preparations had little or no electrophoretic mobility between pH 2 and pH 7.4. The mobile components were ineffective in depressing histamine-induced secretion in dogs with Heidenhain pouches.

The charcoal adsorption procedure previously described for use on human urine was applied to cow urine by Wick & Pauls (99) to prepare an "anti-ulcer factor." Whether bovine "urogastrone" inhibits gastric secretion also is not stated. Patterson and associates in a series of papers (100, 101, 102) reported on the alterations in the excretion of urogastrone produced by extirpation of various endocrine glands of the dog. Thyroidectomy and oophorectomy had little effect while hypophysectomy reduced the excretion of urogastrone. The assays were carried out on dogs receiving histamine and, as with urine extracts from normal dogs, the effects were modified by altering the time interval between histamine and urogastrone injections.

Bucher (103) studied the proteolytic power of urine of women medical students and nurses. The optimum activity on a hemoglobin substrate was at pH 2.0 to 3.4. She concluded that the enzyme, uropepsin, was probably derived from pepsinogen. The output of uropepsin was increased on a high protein diet and decreased on a low protein diet. Balfour *et al.* (104) found that uropepsin disappeared from the urine of the rat after total gastrectomy, confirming similar findings by Bucher & Ivy (105) on the cat. From studies by Block *et al.* (106) on human subjects, uropepsin would appear to be absorbed directly into the blood stream from the secreting peptic cells rather than from the gastrointestinal tract after its secretion into the lumen of the stomach. Podore and co-workers (107) could find no correlation between output of uropepsin and the acidity or secretion of urine in man. The uropepsin excretion was generally at its minimum during the

night and was lower in children than adults. Cats receiving histamine-caffeine in beeswax were kept on low or high protein diets by Bucher & Anderson (108) and the excretion of uropepsin measured. They concluded that the output of the enzyme in the urine was more closely related to protein consumption than to the stimulation of gastric secretion by histamine-caffeine. Such a finding could be anticipated if uropepsin originates from peptic glands and histamine-caffeine stimulates peptic cells only minimally.

Lehmann, Rossiter & Walters (109) studied the influence of riboflavin on hydrochloric acid production in prisoners of war suffering from either postdysenteric debility or starvation syndrome. All showed subnormal hydrochloric acid secretion before treatment. The gastric response to oatmeal gruel and histamine improved following daily riboflavin administration.

Chernov & Pil'don (110) found that caffeine, but not theobromine, stimulated gastric secretion from the Heidenhain pouch. In dogs with Pavlov pouches, however, the conditions were reversed.

In the human stomach Landboe-Christensen & Plum (111) found the intrinsic antianemic factor of Castle present in the fundus. This distribution is different from that in the hog stomach where most of the intrinsic factor is localized in the pyloric part. The alimentary leucocytosis which is absent in pernicious anemia is restored by feeding gastric mucosal extract (112). The gastric juice of infants and children is capable of destroying vitamin A (113). The destruction of carotene and vitamin A in the rat stomach was attributed by Sherman (114) to the presence of carotene oxidase in the gastric mucosa. Hollan (115) found urease present in the gastric juice and mucosa of patients with anacidity or hypoacidity, but none in that of subjects with normal or high acidity. The use of physicochemical methods in the study of the "digestive capacity" of the stomach has been advocated but no data are given (116).

Pancreas

A modification of Dragstedt's pancreatic fistula has been devised by Baronofsky (117) designed to prevent loss of pancreatic juice in the intervals between observations.

Chodnik (118) has studied the cytology of the pancreas in chickens and finds that the secretory granules first appear in close association with the Golgi apparatus. He also noted asynchronous functioning of acini, some becoming depleted while others retained

their granules. Harper & Mackay (119) found that both pancreozymin and vagus nerve stimulation caused discharge of granules from the acinous cells of the pancreas and increased the enzyme content of the juice. Atropine paralyzed the secretory vagus but had no effect on the action of pancreozymin. Atropine also prevents the vacuolization of the acinous cells that commonly follows administration of pilocarpine and acetylcholine (120.)

Neither secretin nor pancreozymin increased the alkaline phosphatase output of the pancreas in experiments by Wang & Grossman (121). Their suggestion that the duct cells may be the source of phosphatase was supported by histological evidence. Their observation that the output of enzymes could not be increased by increasing the dose of secretin is contrary to the current view based on experiments by Barrington in Babkin's laboratory (277).

Véghelyi (122) found pancreatic enzymes practically absent in subjects with nutritional edema studied during the siege of Budapest; necropsy revealed pancreatic fibrosis. Pancreatic secretion returned to normal on a diet adequate in complete protein, especially milk. According to Le Breton & Pantaleon (123) pancreatic juice contains cholesterol esterase and lecithinase.

In a study of the relation between pancreatic secretion and the pH of the duodenal contents Pincus and associates (124) found, as have many others, that the pH of the duodenal contents is decreased by about one unit when pancreatic juice is excluded. More important is their surprising observation that the volume of pancreatic juice secreted during a measured time interval bore no consistent relation to the pH of the duodenal contents during that time. More study will be necessary to validate the concept implied in this observation. In a study of one vagotomized dog Pincus *et al.* (125) noted a decrease after vagotomy of 60 to 80 per cent in the enzyme output of the pancreas during digestion of meals. Delayed gastric emptying doubtless played a part in these results.

Lagerlöf (126) finds that morphine decreases the amount of bile and pancreatic juice delivered to the intestine during the action of secretin. King and associates (127) found that the gastric juice in amounts likely to enter the duodenum during a secretin test, even if the stomach is not drained, does not alter the activity of the pancreatic enzymes sufficiently to obscure the clinical significance of the test.

Edman & Ågren (128) report a new analysis of the "secretin molecule" performed on a sample of secretin phosphate prepared from their crystallized picrolonate. Amino acids were found in proportions indicating a minimum molecular weight of 5,250. The value for total sulfur and cystine however suggests a molecular weight of double the minimum value. An improved method of preparing purified amorphous secretin was announced but not described (129).

Lombroso & Bocchiotti (130) report that the rapid reversible disappearance of lipoids from autolyzing liver tissue (lipodieresis) fails to occur if the liver is obtained from pancreatectomized dogs. Removal of the head of the pancreas, the whole duodenum, and part of the stomach does not necessarily impair nutrition if the subjects receive a high caloric diet low in fat according to Wollaeger *et al.* (131). Douglas & Pratt (132) find that folic acid is of no value in promoting absorption of fat and nitrogenous substances in dogs deprived of pancreatic juice by ligation of the ducts.

Pancreatic extracts prepared by Dragsted's method and by Chaikoff's method were compared in experiments by Canepa & Ivy (133) with respect to their ability to prevent fatty livers in rats on a high fat, low protein diet. Fatty livers developed in the controls and in the rats on Chaikoff's extract but not in those on Dragsted's extract. Bottin (134) presents evidence that the pancreatic juice plays an essential part in the rapidly fatal effects of high intestinal obstruction.

Experimental pancreatitis.—In an interesting study of the possible etiology of acute pancreatic necrosis Tejerina-Fotheringham (135) injected dog bile, human bile, and activated pancreatic juice into the pancreatic ducts of dogs and then ligated the ducts. Dog bile caused necrosis but human bile did not. The author thinks the high concentration of cytotoxic taurocholate in dog bile explains the necrosis. Lium & Maddock (136) induced pancreatic necrosis in cats by ligating the ducts and stimulating the gland by administration of pilocarpine, physostigmin, acetylcholine, or secretin. Obstruction of the ducts after a meal would provide a similar situation in the human. Popper & Necheles (137) found that clamping the upper pancreatic artery in the presence of pancreatic edema caused the edema to progress to necrosis; in their opinion arterial spasm may be a factor in pancreatic necrosis.

Baggenstoss and associates (138) make the interesting suggestion that fibrocystic disease of the pancreas may be due to failure

of the secretin mechanism. They succeeded in extracting secretin from the upper intestinal tract of adults and children in all but two cases, one of chronic intestinal obstruction in an adult and one of fibrocystic disease in a child.

Small Intestine

Motility.—It may be necessary to revise our concept of the effects of somatic and emotional stimuli on duodenal motility as a result of the observations of Mathur, Grindlay & Mann (139) on dogs with exteriorized loops of the duodenum and jejunum covered with skin. The duodenum was found to be generally quiescent in the fasting state. Contrary to our current preconceptions, duodenal motility was initiated or increased by sight or smell of food, the excitement of leaving the cage, stroking the skin, petting the animal, or by sudden noise. Before vomiting the duodenum was quiescent at first but just preceding the act powerful contractions developed, first in the jejunum and then in the second and first portions of the duodenum in that order. Brunaud & Labouche (140) find that longitudinal muscle fibers of the horse duodenum suspended in oxygenated glucose-Tyrode's solution exhibit a prolonged contraction when exposed to low concentrations of epinephrine. The effect was inhibited by F933 or ergotoxin but not by atrophine.

Sokalchuk and associates with Oppenheimer (141) found that the intestinal hypermotility, which is regularly induced by rapid intravenous injection of acid or enzyme hydrolysates of protein, occurred less frequently with a mixture of essential amino acids and glycine (Merck's "VUJ" mixture). The hyperglycemia which follows intravenous administration of amino acid mixtures was not observed after vascular exclusion of the liver. Helm and others (142) recorded intestinal motility by a balloon kymograph method in human subjects. The authors state that the tone and activity of the intestine were decreased during sleep.

Van Liere and his associates (143) found to their considerable surprise that anoxic anoxia of a degree which does not affect the propulsive motility of the intestine in dogs profoundly depresses it in rats and mice. Northup, Stickney & Van Liere (144) found that breathing 6 to 8 per cent carbon dioxide slowed down intestinal motility in the dog. Breathing pure oxygen at one and two atmospheres pressure inhibited intestinal motility in rabbits in four to five and three hours respectively in the experiments of

Troell (145). He also studied the rate of diffusion of various gases from closed loops of the intestine. Increased pressure and increased carbon dioxide concentration in the infused gas increased the rate of diffusion.

As a result of his study of the mysenteric reflex in the dog and rabbit Bozler (146) concludes that the individual rhythmic contractions of the intestinal muscle are myogenic but the strength of the contractions can be modified by an enteric reflex mechanism. This mechanism, in his opinion, conducts impulses chiefly orally. Reid & White (147) found the normal propulsive motility of the guinea pig intestine to be much more rapid than in other laboratory animals.

In a lengthy paper which deals for the most part with controversial pharmacologic problems Emmelin & Feldberg (148) reported that they could find no evidence that histamine, potassium, or barium increases the synthesis of acetylcholine by the excised intestine as claimed by Ambache (278).

According to Chapman, Stanbury & Jones (149) tetraethylammonium causes immediate and profound inhibition of intestinal motility in man which outlasts the blood vascular changes. Abdominal pain was relieved but could still be elicited by distention with a balloon, hence pain fibers were not paralyzed. Collins (150) finds that tetraethylammonium increases the response of the isolated guinea pig ileum to angiotonin and to histamine. Whitrock (151) reports that the denervated small intestine is more sensitive than normal intestine to inhibition by epinephrine, atropine, and tetraethylammonium.

Ambache (152) recorded the electrical activity associated with "pendulum movements" in an isolated preparation of mammalian gut. There is first a slow diphasic wave, "A," followed by a polyphasic response, "B." Both responses persist after doses of nicotine which paralyze the ganglion cells. When the movements are inhibited the "B" response disappears but the "A" response persists.

Secretion.—The removal of metabolic waste products by irrigation of the small intestine has been attempted in dogs following nephrectomy (153, 154) and in patients with renal insufficiency and uremia (155, 156, 157). Large amounts of urea were removed and the azotemia reduced by the lavage. In experimental animals the jejunum was previously reported by others to be a better site for dialysis than other regions of the small intestine, while in

man colonic lavage is now found to be of doubtful value (158). The procedure appears promising in cases where renal damage is not irreversible, but further studies directed towards improvement in the composition of the perfusion fluid are needed.

In a cytological study of the fowl intestinal epithelium Chodnik (159) observed the secretory granules to arise in close association with the Golgi apparatus. The latter undergoes marked changes on contact of the epithelium with food. The secretion of the goblet cells was found to be autonomous and not associated with digestion processes.

Granick & Michaelis (160) in a case of hemochromatosis found ferratin in adequate amounts in the liver and duodenum and concluded that this disease is not due to a defect in ferratin formation in the duodenal mucosa.

Bocchiotti *et al.* (161) prepared duodenal extracts by the method of Zunz & LaBarre and found that those from the hen had a hypoglycemic action in the dog ten or more times that of those prepared from the pig.

Absorption.—Evidence that water is absorbed more slowly from the intestinal tract of the newborn rat than the adult was provided by Heller (162). In pigs with experimentally induced gastric achylia and hypochylia the absorption of nitrogen, fat, carbohydrate, calcium, and phosphorus were essentially normal. Addition of vitamin D increased the absorption of these substances.

Van Liere, Stickney & Northup (163, 164) concluded that the absorption of saline and fluid from intestinal loops of the dog was proportional to the systemic blood pressure. Carotid sinus denervation (raising the arterial pressure to 150 to 190 mm.) increased absorption, while carotid sinus stimulation reduced absorption. The same authors reported (165) that hemorrhage favored absorption of isotonic saline solutions but that this was nullified by the addition of sodium sulfate solution to the intestinal loop. In calcium balance experiments on six healthy individuals Millis & Reed (166) found no evidence that sodium alginate interferes with calcium absorption.

Hahn and others (167) concluded that the increase in hemoglobin formation by administration of a liver fraction was not secondary to increased iron absorption but was a summation response. Gilman & Ivy (168) made a histological study of the guinea pig intestinal epithelium following administration of iron. They noted free diffusion of iron through the epithelial cells into

the lymphatics, formation of iron-protein complex granules in the epithelial cells, and assimilation of the granules with absorption of the dissolved iron via the lymphatics and phagocytes. They noted an increase in the rate of iron absorption in the presence of a sterile abscess. This contradicts the conclusions of Hahn *et al.* (279) based on finding a decreased incorporation of radioactive iron into hemoglobin in the presence of sterile turpentine abscesses. The generally accepted view that the ferrous form is more readily absorbed than the ferric form is explained by Lederer (169) as being due to the greater dialyzability of the former at the pH usually found in the small intestine; however, in the guinea pig at least, ferrous iron is immediately converted to ferric iron and is absorbed as such (168). In the rat intestinal loop ferrous iron is absorbed only as long as the pH is below 6.1; the addition of reducing agents and many organic acids promoted iron absorption (170). In fifteen patients with partial gastric resection studied six days to almost six years after operation Bracci & Bolletti (171) found the resulting anemia proportional to the amount of stomach removed. They believe that there is in the normal gastric mucosa a factor which favors fixation and maintenance of iron.

Ferric citrate but not copper sulfate was found toxic to rats kept on a diet low in protein and choline (172). Addition of protein, but not choline, to the diet prevented all evidence of iron toxicity.

Using iron retention as an index of iron absorption, Frenchman *et al.* (173) concluded that the addition of beef to a basal diet containing iron promoted the absorption of the dietary iron. Hegsted and others (174) found that rats on a diet composed mainly of corn grits deposit ten to twenty times as much iron in the liver as rats on an adequate diet containing the same amount of iron. No distinction appears to have been made between intestinal absorption and utilization. Sharpe & co-workers (175) found the maximum radioactivity of hemoglobin to be reached within ten days after oral administration of radioactive iron. However, Dubach & co-workers (176) point out that accepting the percentage of a test dose of iron which becomes incorporated with circulating hemoglobin as an index of iron absorption is not warranted. Using radioactive iron, they found that only in afebrile patients with hypochromic anemia was such an assumption valid.

Sols & Ponz (177) describe a method of studying intestinal absorption by perfusing a loop of intestine cannulated at both

ends. Glucose absorption is reported to decrease with increase in body weight (178). Larralde (179) reported that as the length of fasting increased there was in the rat a corresponding decrease in the rate of glucose absorption with a levelling off after one hundred and twenty hours' fasting. From the use of various drugs on anesthetized cats with intestinal loops, the conclusion has been drawn that the autonomic nervous system may influence glucose absorption (180). Martini (181) found glucose absorption from Vella loops of dogs to decrease in successive tests at fifteen-minute intervals; addition of cortin to the glucose solution restored absorption to initial values. According to Basu & Ray (182) thiamine promoted absorption of glucose from intestinal loops in rabbits. Using the isolated loop technique. Campbell & Dawson (183) found 3-ethylglucose to be absorbed from the rat intestine 16 per cent rapidly than glucose. In the cat absorption of 3-methylglucose from the intestine took place even when its concentration in the blood was maintained at higher levels than in the intestine. The authors believe their experiments cast doubt on the "phosphorylation theory" of glucose absorption.

The paper chromatographic technique was used in the dog by Dent & Schilling (184) in the study of protein absorption. Portal blood, jugular blood, and urine were examined from one to five hours after feeding various proteins. Ground beef, casein, casein hydrolysate, and human serum albumin were absorbed mainly, if not entirely, as free amino acids. In contrast, dog's plasma protein was absorbed from the intestine without corresponding changes in blood amino acid levels. This suggests that dog's plasma protein may be absorbed intact but this interpretation does not accord with other work in which homologous plasma was fed. Hess (185) found in the rat that L-methionine was absorbed almost as rapidly as DL-methionine.

According to Frazer (186), the mono- and diglycerides and fatty acids resulting from partial hydrolysis of triglycerides combine with bile salts to emulsify the unhydrolyzed triglycerides. Dispersed triglyceride particles of less than 0.5 μ diameter are absorbed as such. Addition of choline to an olive oil-water emulsion facilitated absorption of the oil from the rat intestine. Frazer (187) finds that suitably dispersed paraffin can be absorbed from the intestine but this is denied by Lundbaek & Maaløe (188). In normal individuals more than 95 per cent of a 50-gm. fat meal is

absorbed but in sprue absorption is reduced to 60 to 70 per cent (187); essentially similarly decreased fat absorption was found among British soldiers in India who acquired tropical sprue (189). In early tropical spure large doses of liver parenterally improved the character of the stools but only slowly increased fat absorption (190). Cooke and others (191) studies forty-five cases of idiopathic steatorrhea and concluded that the resemblance of the blood picture to pernicious anemia was only superficial and that the macrocytic anemias of steatorrhea cannot be explained by a unitarian theory applied to macrocytic anemias in general.

Hoffman, Masson & Desbarats (192) found that exclusion of bile from the rabbit intestine did not interfere with the absorption of the lipid-soluble steroid hormones administered by stomach tube. Heersma & Annegers (193) found in bile-fistula dogs that fat absorption was accelerated by the incorporation in the diet of fresh ox bile; surprisingly enough desiccated ox bile, bile salts, and other bile preparations were ineffective. Desiccation of fresh bile greatly reduced its effectiveness in preventing steatorrhea.

In an interesting experiment involving the use of radioactive phosphorus, Zilversmit, Chaikoff & Entenman (194) demonstrated that phospholipids are not obligatory intermediates participating in fat transport across the intestinal wall in the dog and rat. Phospholipids labelled with radioactive phosphorus were fed to fasting rats by Artom & Swanson (195). The large amounts of inorganic radioactive phosphate in the plasma indicated that the lipid was split in the intestinal tract before absorption. However, the presence of detectable amounts of the ingested phospholipid in the serum demonstrated that the intact molecule was also absorbed.

Bollman & Flock (196) find in the rat that the cholesterol absorption via lymphatics is extremely small compared with the absorption of fat. Analyses of intestinal lymph by Flock & Bollman (197) showed no differences in alkaline phosphatases in rats on fat and fat-free diets. Although intestinal mucosa has a high content of phosphatase, it did not appear to be a source of the plasma alkaline phosphatase.

A roentgenologic method for the study of fat absorption has been described by Groen (198). The contrast shadow of the intestine after oral administration of iodized oil (lipiodol) is studied on x-ray films taken at regular intervals. Alimentary lipemia is

potentiated by the administration of heparin and synthetic anticoagulants (199). This phenomenon is being used experimentally as a test for intestinal absorption fat.

In the rat the greatest absorption of ingested vitamin A occurs from the jejunum (200). In man carotene absorption from vegetable foods occurs only when the vegetable cell membrane is destroyed; addition of fat increases absorption only if the carotene has already been liberated from the cell (201, 202). In young rats vitamin A absorption, as judged by liver storage, was increased when the vitamin A was given dispersed in water (203). Sobel and co-workers (204) found in newborn infants an impaired intestinal absorption of vitamin A in oil, which could be remedied by using an aqueous dispersion. Emulsions of vitamin A are absorbed better, too (205). In a study conducted by Alexander *et al.* (206) mineral oil was taken for long periods by twenty-five human subjects. From the reduced blood carotene levels the workers concluded that mineral oil reduces the amount of food carotene absorbed.

Interest in the absorbability of orally administered antibiotics continues. Stewart & May (207) report that the greatest intestinal absorption of penicillin in man occurs from the duodenum and jejunum; contrary to earlier workers they find no significant destruction of the penicillin by the acid of the gastric contents. Rose & Spinks (208), from their study on mice, suggest that the poor intestinal absorption of sulfaguanidine derivatives is associated with the chemical structure which permits linking of the compound with a substrate by hydrogen bonds. Oral administration of nicotinic acid to rats increased the absorption of various sulfonamides from the gastrointestinal tract (209); no effect was noted when the nicotinic acid was given subcutaneously.

Séquin (210) found absorption of aminopyrine to be more rapid and at a more uniform rate from intestinal loops of the rat than from rectal loops. The interaction between bile salts and quinine results in the formation of a dialyzable product (211); it is therefore suggested that more effective absorption of quinine from the intestine would be obtained if bile salts were given with the quinine. Various antibodies administered by intragastric inoculation have been shown to be absorbed from the bowel (212). The absorption of aspirin from perfused Thiry-Vella jejunal loops in dogs occurred before it was hydrolyzed (213). Maximum

blood concentrations were reached when the outflowing perfusate was at pH 5.0 to 5.8.

Two papers (214, 215) deal with survival and state of nutrition of patients after massive resection of the small intestine for mesenteric thrombosis; in one patient eighteen inches and in another fourteen inches of jejunum were left. Carbohydrate and protein were tolerated better than fat.

Visceral sensation and reflexes.—Contractions of the rectus muscle on application of mechanical, chemical, thermal, or electrical stimuli to the small intestine in cats were observed by von Euler & Sjöstrand (216). Downman, McSwiney & Vass (217) noted dilation of the pupil, increase in blood pressure, and leg movements when the intestine was stimulated. The mesentery was more sensitive than the intestine since responses were obtained on rubbing the mesentery but not the intestine. Local cooling or freezing were not effective stimuli for the intestine.

In a brief communication Theobald (218) states that visceral pain can be abolished by anesthetizing the cutaneous area to which it is referred; no evidence was cited in the available reference. Grimson and his associates (219) found that removal of the right and part of the left celiac ganglion was effective for most types of visceral pain. Cutting the vagi failed to relieve the pain of the gastric crises of tabes. Holzmann & Sakharova (220) introduced a stimulating electrode into the stomach and measured the chronaxie and electrical threshold (rheobase) for sensation at various points on the mucous membrane. The threshold was lowest along the lesser curvature and highest at the pyloric region. The chronaxie was fairly uniform throughout.

Gregory (221) induced nausea and vomiting in dogs by administering apomorphine and noted motor inhibition and increased secretion in Thiry-Vella loops of small intestine. These local phenomena were unaltered by bilateral splanchicotomy but were abolished by thoracic vagotomy.

Colon

The volume of gas in the digestive tract of the average person was estimated by Blair *et al.* (222) to be about one liter. The amount expelled per day was variable (one subject who ate beans expelled 2,600 cc.) but averaged less than the total volume in the gut. The volume egested depends largely on intestinal motility.

Alstead & Patterson (223) measured the output of flatus in human subjects; physostigmin and prostigmin were found to occasionally increase gas egestion but most effective was the vasopressor fraction of pituitrin. Gas formation in closed intestinal loops of intestine in the cat could be inhibited by most antibiotics, indicating the role of intestinal flora in gas production (224).

The abdominal distension occurring with decrease in atmospheric pressure was studied in animals by Ivanov (225). With intestinal distension by gases there also occurred apnea, convulsions, and cardiovascular irregularities. Denervation of the intestine reduced the changes in blood pressure due to distention; hence the cardiovascular caisson disturbances are probably due to gastrointestinal reflexes. Guest (226) found that the incidence of gas pains at a simulated altitude of thirty-eight thousand feet was not reduced by a bland diet.

Bernhard & Bullet (227) used deuterium to demonstrate that intensive synthesis of fatty acids occurs in the intestinal tract of the white rat on a high carbohydrate diet. From Phillipson's study (228) it is evident that synthesis by bacterial action of volatile fatty acids occurs extensively in the dog's large intestine.

In healthy young adults Shoshkes (229) found the stool to be alkaline when hard but acid when loose. Mouth-rectum transit time had no bearing on fecal pH (average 6.4 to 7.5).

In forty healthy subjects on a 3,000 kilocal diet consisting of varying amounts of lard or hydrogenated vegetable oil, Annegers, Boutwell & Ivy (230) found the total fecal fat excretion unrelated to either the amount of type of fat taken. This indicates that fat-balance "digestibility" studies are of questionable validity.

Wollaeger, Comfort & Osterberg (231) found in young healthy adults that the fecal total solids, nitrogen, and percentage of ingested fat in the feces were the same when the daily fat intake was 101 mg. as when it was 208 gm. The amounts of fat in the feces were greater on the higher fat intake. Undigested dietary fat may be modified by the action of bacteria.

Ulcer and Vagotomy in Experimental Animals

Experimental ulcer.—In acute experiments on dogs Davis & Ivy (232) found that the threshold for thermal injury of the gastric mucosa (65° C.) was above that of the buccal mucosa (55° C.). Consequently gastric ulceration and carcinoma are unlikely to result from thermal irritation.

Curare in large doses produced hemorrhage into the intestine of dogs even when the gastric secretion was excluded (233). The lesions could be prevented by blood transfusions and vasoconstrictor drugs.

Several papers on the role of acid and pepsin in the production of ulcer have been published. Dameron & Wangensteen (234) perfused paired jejunal loops in twelve dogs with gastric juice collected from pouch dogs after stimulation with either histamine or pilocarpine in beeswax. The histamine juice had a higher acidity and lower pH but the pilocarpine juice caused more widespread ulcerations and earlier appearance of blood in the perfusate. Since pilocarpine juice has the greater peptic activity the authors concluded that pepsin is an important factor in ulcer formation. A similar conclusion was drawn by LeVeen (235) who either sprayed or perfused the intestine with solutions of acid or acid and pepsin. The acid-pepsin solution caused more prominent ulcerations and more spasm than acid alone. Primary closure of the Heidenhain pouch in dogs was found by Stern, Grossman & Ivy (236) to result in acute ulcer formation and perforation in all cases; daily aspiration of the pouch contents reduced the incidence of ulceration with perforation. In dogs with double lumen gastrojejunal anastomosis Steinberg & Brunkow (237) found histamine ineffective in producing ulcers, presumably because of more effective neutralization of the gastric acid. Cummins, Grossman & Ivy (238) perfused hydrochloric acid through a gastrostomy into the stomachs of five dogs. All developed ulcers and those tested also showed acidosis. Combatting the acidosis by either intraileal or intravenous administration of sodium bicarbonate reduced sharply the incidence of ulcer formation.

Serum from a horse immunized to several antigens was injected locally into the stomach of dogs by Friesen *et al.* (239). Subsequent injection of any one of the antigens caused prolonged local edema and often ulceration. Histamine in beeswax caused ulcers in the edematous stomach more readily than in normal. Three papers by Lillehei, Wangensteen, and collaborators (240, 241, 242) pertain to factors which abet ulcer formation in dogs by chronic histamine in beeswax injections. Susceptibility to ulceration was found to be increased by age, muscular fatigue, anemia, and shock. The combined effects of posthemorrhagic anemia and shock on the ulcer diathesis were synergistic.

LeVeen (243) found that ligation of the gastric arteries in the

dog reduced the secretory response to histamine as well as the formation of histamine-induced ulcers. Extensive ligation was found to result in ulcers. In a similar study, Baronofsky (244) found that ligation of the gastric arteries did not protect against histamine-induced ulcers.

A new antihistaminic drug was found by Winter & Mushett (245) not to prevent in dogs either the gastrointestinal lesions or the hematologic effects of histamine. By protecting against the acute lethal effects of histamine the antihistaminic drug permitted the use of larger doses of histamine with reduction in the time necessary to produce the ulcers.

In dogs with operative defects and sutured incisions of the gastric mucosa, Price (246) determined that almost complete mucosal healing occurred within six or seven days. Healing was incomplete after twelve days in dogs receiving histamine in beeswax. The delay in mucosal repair is attributed to the deleterious effect of the histamine-induced hypersecretion, but it may have been due to the vascular effects of histamine.

The ulcer which forms in the rat rumen after pylorus ligation has received attention from several investigators since its healing has been the objective in procedures for assaying antiulcer substances. Pauls *et al.* (247) found that old rats are more resistant to ulceration than young rats and that sex was not a factor in resistance in young animals. They failed to find a correlation between either volume or acidity of the juice and degree of ulceration and concluded that peptic activity was probably the most important ulcergenic factor. This conclusion is in agreement with that of Shay, Komarov, and collaborators (280) who found that the severity of ulceration after pyloric ligation was proportional to the peptic activity of the gastric contents. Prevention of ulcer formation in the rat with pylorus ligation by vagotomy (248) and by oral or parenteral administration of *o*-hydroxybenzoic (salicylic) acid (249), aluminum dihydroxyaminoacetate (250) and tetraethylammonium chloride (251) has been reported.

Risley, Raymond & Barnes (252) tested on rats with ligation of the pylorus the antiulcer properties of a salt cake made by treating intestine with "0.4 per cent concentrated hydrochloric acid " (*sic!*), "enterogastrone," urine extract, and "urogastrone" and found the potency to increase in the order listed. In dogs subjected to the Mann-Williamson operation, Saltzstein and coworkers (253) found that 4 gm. of "enterogastrone" per day given

orally reduced the incidence of ulcer formation from 100 per cent to 79 per cent and prolonged the postoperative survival time in all dogs; however, the results were not as favorable as those reported by Ivy in 1946 in a similar series.

Experimental ulcers induced by feeding cinchophen were reported to be prevented by parenteral administration of ascorbic acid (254) and stilbestrol (255) but not by vagotomy (256, 257). Hilsabeck & Hill (257) believe that the cinchophen ulcer is produced by inactivation of a protective mechanism normally operating in the stomach. De Muro & Ficari (258) noted that following the administration of large doses of desoxycorticosterone (DCA) to dogs and rabbits, there developed pathologic changes in the stomach and intestine, including atrophy of the mucosa and degeneration of the muscle. The treatment of peptic ulcer with DCA therefore has no basis since the decrease in gastric secretion is not a physiological response but the result of mucosal atrophy.

In guinea pigs mucosal lesions of the upper gastrointestinal tract, and in cats ulcers and gastroduodenitis, were found by Merendino (72) when the animals were given morphine sulfate in beeswax. Egg white lysozyme when applied topically to a Pavlov pouch removed the surface mucus and caused "small ulcerated lesions" (259). According to Hanrahan (260), viable implants of the jejunum in the stomach do not become ulcerated unless the expulsion of gastric contents and duodenal regurgitation are interfered with.

Vagotomy in experimental animals.—Vanzant (261) studied gastric motility and secretion in ten dogs over a period of sixteen to fifty-seven months after transthoracic vagotomy. Both motor and secretory functions were initially depressed but eventually returned to normal, except for the secretory response to histamine which remained below normal by 20 to 80 per cent in terms of volume. A similar effect of vagotomy on the secretory response to histamine in dogs and humans was reported by Oberhelman & Dragstedt (262) and in dogs by Woodward, Dragstedt and others (263).

Robertson & Grossman (264) found that whereas prostigmine or urecholine caused little secretion of acid by the vagotomized whole stomach pouch in dogs, these drugs produced a marked potentiation of the secretory effect of histamine. As they point out, this observation has important implications for the understanding of the effects of atropine and of vagotomy on the action

of secretory stimulants. Feldman & Morrison (265) report that thyroid, prostigmine, mecholyl, acetylcholine, and carbamylcholine chloride (Doryl) accelerated gastric emptying after vagotomy. Acetylcholine and Doryl were the more effective.

Conflicting results with vagotomy are reported on Mann-Williamson ulcers. Harkins, Hooker and others (248, 266) found the incidence of ulcers in Mann-Williamson dogs reduced by vagotomy from a control level of 80 per cent to 11 per cent. On the other hand Oliver (267) and Saltzstein, Sandweiss, and their co-workers (268) found vagotomy of no benefit. Harkins *et al.* (248, 266) also report that vagotomy does not prevent histamine ulcers in guinea pigs but does prevent the development of ulcers of the rumen in rats with pyloric ligation.

Snape (269) found that vagotomy delayed but did not prevent emptying of the gall bladder in dogs in response to various intestinal stimuli, including cream and fatty acids; the response to cholecystokinin was unaffected (270). Jefferson & Necheles (40) noted in vagotomized dogs marked gaseous distention of the stomach and intestine which was relieved somewhat by left phrenicotomy.

LITERATURE CITED

1. Goetzl, F. R., and Stone, F., *Gastroenterology*, **9**, 444–53 (1947)
2. Goetzl, F. R., and Stone, F., *Gastroenterology*, **10**, 708–13 (1948)
3. Donhoffer, S., and Vonotzky, J., *Am. J. Physiol.*, **150**, 329–33 (1947)
4. Donhoffer, S., and Vonotzky, J., *Am. J. Physiol.*, **150**, 334–39 (1947)
5. Scott, E. M., and Verney, E. L., *J. Nutrition*, **34**, 401–8 (1947)
6. Scott, E. M., and Verney, E. L., *J. Nutrition*, **34**, 471–80 (1947)
7. Lundbaek, K., and Stevenson, J. A. F., *Am. J. Physiol.*, **151**, 530–37 (1947)
8. Vartiainen, I., and Bastman-Heiskanen, L., *Ann. Med. Intern. Fenniae*, **36**, 740 (1947)
9. Soulairac, A., *Compt. rend.*, **224**, 961–63 (1947); *Chem. Abstracts*, **41**(15) 4843 (1947)
10. Hanson, M. E., and Grossman, M. I., *Federation Proc.*, **7**, 50 (1948)
11. Hoelzel, F., *Am. J. Digestive Diseases*, **14**, 401–4 (1947)
12. Adolph, E. F., *Am. J. Physiol.*, **151**, 110–25 (1947)
13. Richter, C. P., and Hall, C. E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 561–66 (1947)
14. Ginsberg, R. S., Feldman, M., and Necheles, H., *Gastroenterology*, **10**, 281–85 (1948)
15. MacDonald, R. M., Ingelfinger, F. J., and Belding, H. W., *New England J. Med.*, **237**, 887–96 (1947)
16. Harris, S. C., Ivy, A. C., and Searle, L. M., *J. Am. Med. Assoc.*, **134**, 1468–75 (1947)
17. Holmes, J. H., and Gregersen, M. I., *Am. J. Physiol.*, **151**, 252–57 (1947)

18. KLIORIN, A. I., *Byull. Eksptl. Biol. Med.*, **24**, 200–2 (1947); *Chem. Abstracts*, **42**(9), 3076 (1948)
19. KOROPOV, V. M., *Arkh. Patol.*, **9**, 59–66 (1947); *Brit. Abstracts*, AIII, 240 (1948)
20. YONKMAN, F. F., *Am. J. Digestive Diseases*, **14**, 360–63 (1947)
21. ZIPKIN, I., *Science*, **106**, 343 (1947)
22. FISCHMANN, E. J., AND FISCHMANN, A., *J. Lab. Clin. Med.*, **33**, 757–76 (1948)
23. LURA, H. E., *J. Dental Research*, **26**, 203–24 (1947)
24. JUNQUEIRA, L. C. U., RABINOVITCH, M., AND FAJER, A. B., *Rev. brasil. biol.*, **7**, 435–38 (1947); *Chem. Abstracts*, **42**(8), 2662 (1948)
25. EHRICH, W. E., AND SEIFTER, J., *Arch. Path.*, **45**, 239–45 (1948)
26. KRASNOVSKAYA, L. A., AND EFIMOV, V. V., *Byull. Eksptl. Biol. Med.*, **24**, 104–5 (1947); *Chem. Abstracts*, **42**(9), 3075 (1948)
27. STEWART, W. C., *Am. J. Physiol.*, **152**, 1–5 (1948)
28. TEMPLETON, F. E., *Gastroenterology*, **10**, 96–101 (1948)
29. HWANG, K., *Federation Proc.*, **7**, 59–60 (1948)
30. BRODY, D. A., LAWSON, J. D., AND QUIGLEY, J. P., *Federation Proc.*, **7**, 13 (1948)
31. HWANG, K., AND UNNA, K. R., *Federation Proc.*, **7**, 229–30 (1948)
32. BRODY, D. A., AND QUIGLEY, J. P., *Gastroenterology*, **9**, 570–75 (1947)
33. HENSCHEL, A., KEYS, A., STURGEON, M., AND TAYLOR, H. L., *Am. J. Physiol.*, **149**, 107–11 (1947)
34. ANNEGERS, J. H., AND IVY, A. C., *Am. J. Physiol.*, **150**, 461–65 (1947)
35. ANNEGERS, J. H., AND IVY, A. C., *Gastroenterology*, **8**, 711–16 (1947)
36. NIMEH, W., *Rev. Gastroenterol.* (N. Y.), **14**, 763–75 (1947)
37. VÉGHELYI, P., *Ann. Paediat.*, **168**, 93–104 (1947)
38. NORTHUP, D. W., AND VAN LIERE, E. J., *J. Pharmacol. Exptl. Therap.*, **93**, 208–9 (1948)
39. SHAPIRO, K. L., AND IVY, A. C., *Federation Proc.*, **7**, 112 (1948)
40. JEFFERSON, N. C., AND NECHELES, H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 166–69 (1948)
41. FELDMAN, M., AND MORRISON, S., *Am. J. Digestive Diseases*, **15**, 175 (1948)
42. PATTERSON, T. L., AND SCANTLEBURY, R. E., *Rev. can. biol.*, **6**, 171–72 (1947)
43. BRODY, D. A., AND QUIGLEY, J. P., *Federation Proc.*, **7**, 13–14 (1948)
44. SINGH, I., AND SINGH, S. I., *Current Sci.* (*India*), **16**, 259–60 (1947); *Chem. Abstracts*, **42**(5), 1649 (1948)
45. SWENSON, P. C., AND MANGES, W. E., *Radiology*, **50**, 365–77 (1948)
46. BRADFORD, N. M., AND DAVIES, R. E., *Biochem. J.*, **42**, P XII (1948)
47. DAVENPORT, H. W., *Gastroenterology*, **9**, 293–302 (1947)
48. DAVIES, R. E., AND TERNER, C., *Biochem. J.*, **42**, XIII (1948)
49. DAVIES, R. E., LONGMUIR, N. M., AND CRANE, E. E., *Nature*, **159**, 468–69 (1947)
50. HORSTMANN, P., *Acta Physiol. Scand.*, **14**, 27–42 (1947)
51. LINDE, S., TEORELL, T., AND ÖBRINK, K. J., *Acta Physiol. Scand.*, **14**, 220–32 (1947)
52. TEORELL, T., *Gastroenterology*, **9**, 425–43 (1947)
53. KELLER, R., AND PISHA, B., *Rev. Gastroenterol.* (*N. Y.*), **14**, 495–501 (1947)
54. KURTZ, L. D., AND CLARK, B. B., *Gastroenterology*, **9**, 594–602 (1947)
55. HOFSTETTER, T., *Gastroenterologia*, **72**, 201–15 (1947)

56. HOKIN, L. E., AND REHM, W. S., *Am. J. Physiol.*, **151**, 380–90 (1947)
57. SCHIFF, L., STEVENS, C. D., MOLLE, W. E., STEINBERG, H., KUMPE, C. W., and STEWART, P., *J. Natl. Cancer Inst.*, **7**, 349–54 (1947)
58. SELLE, W. A., AND MILLER, O. B., *Federation Proc.*, **7**, 110 (1948)
59. FORSGREN, E., *Acta Med. Scand.*, **128**, 281–88 (1947); *Chem. Abstracts*, **41**, (22), 7503 (1947)
60. KOWALEWSKI, K., *Acta Gastro-Enterology (Belgium)*, **10**, 503–15 (1947)
61. KARP, D., *Gastroenterology*, **9**, 790–93 (1947)
62. BABKIN, B. P., AND LAWSON, R. N., *Acta Med. Scand.*, Suppl. **196**, 308–21 (1947)
63. KARP, D., AND LAWSON, R. N., *Rev. can. biol.*, **7**, 187 (1948)
64. REED, J. A., *Gastroenterology*, **10**, 118–19 (1948)
65. PALMER, E. D., *Am. J. Digestive Diseases*, **14**, 342–45 (1947)
66. BANDES, J., HOLLANDER, F., AND BIERMAN, W., *Gastroenterology*, **10**, 697–707 (1948)
67. STRÖM, G., AND UVNÄS, B., *Acta Physiol. Scand.*, **15**, 6–10 (1948)
68. CLARK, B. B., *Gastroenterology*, **9**, 454–60 (1947)
69. GROSSMAN, M. I., ROBERTSON, C. R., AND ANDERSON, W. L., *Federation Proc.*, **7**, 46 (1948)
70. BABKIN, B. P., AND KARP, D., *Can. Med. Assoc. J.*, **56**, 137–41 (1947)
71. BLOCK, M., BACHRACH, W. H., MASON, J. W., AND POLLARD, H. M., *Am. J. Med.*, **3**, 119–20 (1947)
72. MERENDINO, K. A., *Gastroenterology*, **10**, 504–39 (1948)
73. BROWN, H. S., POSEY, E. L., AND GAMBILL, E. E., *Gastroenterology*, **10**, 837–47 (1948)
74. ZWEIG, M., STEIGMANN, F., AND MEYER, K. A., *Federation Proc.*, **7**, 268 (1948)
75. ROSSIEN, A. X., *Am. J. Digestive Diseases*, **14**, 205–7 (1947)
76. ROSSIEN, A. X., *Rev. Gastroenterol. (N. Y.)*, **14**, 623–38 (1947)
77. LITTMAN, A., AND GROSSMAN, M. I., *Federation Proc.*, **7**, 73–74 (1948)
78. CLARK, B. B., AND ADAMS, W. L., *Gastroenterology*, **9**, 284–92 (1947)
79. HALE, E., AND GROSSMAN, M. I., *Federation Proc.*, **7**, 48 (1948)
80. CODE, G. F., HALLENBECK, G. A., AND GREGORY, R. A., *Am. J. Physiol.*, **151**, 593–605 (1947)
81. CAMPORI, A. S., *Rev. med. y cienc. afines (Buenos Aires)*, **9**, 355–65 (1947)
82. HOLLANDER, F., LAUBER, F. U., AND STEIN, J., *Am. J. Physiol.*, **149**, 724–31 (1947)
83. HOLLANDER, F., AND LAUBER, F. U., *Federation Proc.*, **7**, 56–57 (1948)
84. WOLF, S., AND WOLFF, H. G., *Gastroenterology*, **10**, 251–55 (1948)
85. MORTON, G. M., AND STAVRAKY, C. W., *Federation Proc.*, **7**, 82 (1948)
86. KOMAROV, S. A., SHAY, H., AND SIPLET, H., *Federation Proc.*, **7**, 67 (1948)
87. GLASS, G. B. J., AND BOYD, L. J., *Rev. Gastroenterol. (N. Y.)*, **15**, 396–414 (1948)
88. GLASS, G. B. J., AND BOYD, L. J., *Rev. Gastroenterol. (N. Y.)*, **15**, 511–19 (1948)
89. TULIN, M., GUTMANN, J., AND ALMY, T. P., *Gastroenterology*, **9**, 191–97 (1947)
90. GOULD, J. C., AND KING, H. K., *Biochem. J.*, **41**, xxi (1947)
91. EDWARDS, L. E., AND EDWARDS, C. T., *Federation Proc.*, **7**, 30 (1948)
92. JALLING, D., AND JORPES, E., *Acta Physiol. Scand.*, **13**, 231–37 (1947)

93. Friedman, M. H. F., and King, E. N., *Federation Proc.*, **6**, 107 (1947)
94. Uvnäs, B., *Acta Physiol. Scand.*, **15**, 1–5 (1948)
95. Kirsner, J. B., Levin, E., and Palmer, W. L., *Gastroenterology*, **10**, 256–73 (1948)
96. Visscher, F. E., *Federation Proc.*, **7**, 128 (1948)
97. Katz, J., Dryer, R. L., Paul, W. D., and Routh, J. I., *Federation Proc.*, **7**, 163 (1948)
98. Öbrink, K. J., *Experientia*, **3**, 455–56 (1947); *Chem. Abstracts*, **42**(10), 3445 (1948)
99. Wick, A. N., and Pauls, F., *Federation Proc.*, **7**, 133–34 (1948)
100. Kaulbersz, J., Patterson, T. L., Sandweiss, D. J., and Saltzstein, H. C., *Am. J. Physiol.*, **150**, 373–80 (1947)
101. Patterson, T. L., Kaulbersz, J., Sandweiss, D. J., and Saltzstein, H. C., *Rev. can. biol.*, **7**, 192–93 (1948)
102. Patterson, T. L., Kaulbersz, J., Sandweiss, D. J., and Saltzstein, H. C., *Federation Proc.*, **7**, 91 (1948)
103. Bucher, G. R., *Gastroenterology*, **8**, 627–47 (1947)
104. Balfour, D. C., Preston, F. W., and Bollman, J. L., *Gastroenterology*, **10**, 880–82 (1948)
105. Bucher, G. R., and Ivy, A. C., *Am. J. Physiol.*, **150**, 415–19 (1947)
106. Block, S., Rosenberg, L., Broh-Kahn, R. H., and Mirsky, I. A., *Federation Proc.*, **7**, 9 (1948)
107. Podore, E. J., Broh-Kahn, R. H., and Mirsky, I. A., *Federation Proc.*, **7**, 95 (1948)
108. Bucher, G. R., and Anderson, A., *Federation Proc.*, **7**, 16–17 (1948)
109. Lehmann, H., Rossiter, R. J., and Walters, J. H., *J. Physiol.* (*London*), **106**, 24–25 (1947)
110. Chernov, V. M., and Pil'don, Z. A., *Farmakol. i Toksikol.*, **10**,(1), 31–36 (1947); *Chem. Abstracts*, **41**(22), 7532 (1947)
111. Landboe-Christensen, E., and Plum, C. M., *Am. J. Med. Sci.*, **215**, 17–23 (1948)
112. Boccuzzi, G., and Paolino, W., *Rev. Gastroenterol.* (*N. Y.*), **14**, 839–50 (1947)
113. Cacioppo, F., and Cascio, G., *Boll. soc. ital. biol. sper.*, **23**, 500–3 (1947); *Chem. Abstracts*, **42**(5), 1646 (1948)
114. Sherman, W. C., *Proc. Soc. Exptl. Biol. Med.*, **65**, 207 (1947)
115. Hollan, S., *Brit. J. Exptl. Path.*, **28**, 365–67 (1947)
116. Cytronberg, S. S., Del Castillo, A. L. A., and De Lachica, A., *Rev. Gastroenterol.* (*N. Y.*), **14**, 721–38 (1947)
117. Baronofsky, I. D., *Surgery*, **23**, 665–69 (1948)
118. Chodnik, K. S., *Quart. J. Microscop. Sci.*, **89**, 75–87 (1948)
119. Harper, A. A., and Mackay, I. F. S., *J. Physiol.* (*London*), **107**, 89–96 (1948)
120. Tucker, A. L., *J. Pharmacol. Exptl. Therap.*, **92**, 421–24 (1948)
121. Wang, C. C., and Grossman, M. I., *Federation Proc.*, **7**, 130–31 (1948)
122. Véghelyi, P. V., *Lancet*, **I**, 497–98 (1948)
123. Le Breton, E., and Pantaleon, J., *Arch. sci. physiol.*, **1**, 63–80 (1947); *Chem. Abstracts*, **42**(7), 2296 (1948)
124. Pincus, I. J., Thomas, J. E., Hausman, D., and Lachman, P. O., *Proc. Soc. Exptl. Biol. Med.*, **67**, 497–501 (1948)

125. PINCUS, I. J., THOMAS, J. E., AND LACHMAN, P. O., *Federation Proc.*, **7**, 94 (1948)
126. LAGERLÖF, H. O., *Acta Physiol. Scand.*, **13**, 306–9 (1947)
127. KING, E. N., FRIEDMAN, M. H. F., AND PINCUS, I. J., *Federation Proc.*, **7**, 64 (1948)
128. EDMAN, P., AND ÅGREN, G., *Arch. Biochem.*, **13**, 283–86 (1947)
129. FRIEDMAN, M. H. F., AND THOMAS, J. E., *Federation Proc.*, **7**, 37 (1948)
130. LOMBROSO, C., AND BOCCHIOTTI, S., *Science*, **107**, 90 (1948)
131. WOLLAEGER, E. E., COMFORT, M. W., CLAGETT, O. T., AND OSTERBERG, A. E., *Proc. Staff Meeting Mayo Clinic*, **23**, 245 (1948)
132. DOUGLAS, G. F., JR., AND PRATT, T. D., *Proc. Soc. Exptl. Biol. Med.*, **68**, 171–74 (1948)
133. CANEPA, J. F., AND IVY, A. C., *Federation Proc.*, **7**, 17 (1948)
134. BOTTIN, J., *Rev. méd Liége*, **2**, 48–49 (1947)
135. TEJERINA-FOTHERINGHAM, W., *Gastroenterology*, **10**, 687–96 (1948)
136. LIUM, R., AND MADDOCK, S., *Federation Proc.*, **7**, 274 (1948)
137. POPPER, H. L., AND NECHELES, H., *Proc. Central Soc. Clin. Research*, **20**, 65 (1947)
138. BAGGENSTOSS, A. H., POWER, M. H., AND GRINDLAY, J. H., *Am. J. Path.*, **24**, 692–93 (1948)
139. MATHUR, P. D., GRINDLAY, J. H., AND MANN, F. C., *Gastroenterology*, **10**, 866–79 (1948)
140. BRUNAUD, M., AND LABOUCHE, C., *Compt. rend. soc. biol.*, **141**, 167–69 (1947)
141. SOKALCHUK, A., ELLIS, D., WEBSTER, M. R., GREISHEIMER, E. M., AND OPPENHEIMER, M. J., *Gastroenterology*, **10**, 831–36 (1948)
142. HELM, J. D., JR., KRAMER, P., MACDONALD, R. M., AND INGELFINGER, F. J., *Gastroenterology*, **10**, 135–37 (1948)
143. VAN LIERE, E. J., CRABTREE, W. B., NORTHUP, D. W., AND STICKNEY, J. C., *Proc. Soc. Exptl. Biol. Med.*, **67**, 331–32 (1948)
144. NORTHUP, D. W., STICKNEY, J. C., AND VAN LIERE, E. J., *Federation Proc.*, **7**, 86 (1948)
145. TROELL, L., *Acta. Chir. Scand. Suppl.* **122**, 95 (1947)
146. BOZLER, E., *Federation Proc.*, **7**, 12 (1948)
147. REID, M. E., AND WHITE, W. C., *Am. J. Physiol.*, **152**, 455–59 (1948)
148. EMMELIN, M., AND FELDBERG, W., *J. Physiol., (London)*, **106**, 482–502 (1947)
149. CHAPMAN, W. P., STANBURY, J. B., AND JONES, C. M., *J. Clin. Invest.*, **27**, 34–38 (1948)
150. COLLINS, D. A., *Federation Proc.*, **7**, 21–22 (1948)
151. WHITROCK, R. M., *Federation Proc.*, **7**, 265 (1948)
152. AMBACHE, N., *J. Physiol. (London)*, **106**, 139–53 (1947)
153. ROGERS, J. W., SELLERS, E. A., AND GORNALL, A. G., *Science*, **106**, 108 (1947)
154. WHITE, B. H., AND HARKINS, H. N., *Proc. Central Soc. Clin. Research*, **20**, 43 (1947)
155. OPPENHEIMER, G. D., ROSENAK, S., *J. Mt. Sinai Hosp., N. Y.*, **14**, 980–11 (1948)
156. ODEL, H. M., AND FERRIS, D. O., *Proc. Staff Meetings Mayo Clinic*, **23**, 201–8 (1948)
157. MALUF, N. S. R., *Federation Proc.*, **7**, 77 (1948)

158. Dougherty, G. W., Odel, H. M., and Ferris, D. O., *Proc. Staff Meetings Mayo Clinic*, **23**, 209–14 (1948)
159. Chodnik, K. S., *Quart. J. Microscop. Sci.*, **88**, 419–43 (1947)
160. Granick, S., and Michaelis, L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 296–98 (1947)
161. Bocchiotti, S., Bellotti, M., and De Langlade, E., *Boll. soc. ital. biol. sper.*, **23**, 270–71 (1947), *Chem. Abstracts* **42**(2), 657 (1948)
162. Heller, H., *J. Physiol. (London)*, **106**, 245–55 (1947)
163. Stickney, J. C., Northup, D. W., and Van Liere, E. J., *Am. J. Physiol.*, **150**, 466–70 (1947)
164. Van Liere, E. J., Stickney, J. C., and Northup, D. W., *Am. J. Physiol.*, **150**, 149–52 (1947)
165. Van Liere, E. J., Northup, D. W., and Stickney, J. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 260–62 (1947)
166. Millis, J., and Reed, F. B., *Biochem. J.*, **41**, 273–75 (1947)
167. Hahn, P. F., Sheppard, C. W., and Carothers, E. L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 173–75 (1947)
168. Gilman, T., and Ivy, A. C., *Gastroenterology*, **9**, 162–69 (1947)
169. Lederer, J., *Arch. intern. pharmaco-dynamie*, **75**, 436 (1948)
170. Groen, J., van den Brock, W. A., and Veldman, H., *Biochim. et Biophys. Acta*, **1**, 315–26 (1947); *Chem. Abstracts*, **42**(8), 2659 (1948)
171. Bracci, U., and Bolletti, A., *Ann. ital. chir.*, **24**, 261 (1947)
172. Hegsted, D. M., Kinney, T. D., and Cartaya, J. A., *Am. J. Path.*, **24**, 722 (1948)
173. Frenchman, R., Boroughs, E. D., and Johnson, F. A., *Federation Proc.*, **7**, 287 (1948)
174. Hegsted, D. M., Finch, C. A., and Kinney, T. D., *Federation Proc.*, **7**, 290 (1948)
175. Sharpe, L. M., Harris, R. S., Peacock, W. C., and Cooke, R. C., *Federation Proc.*, **7**, 112 (1948)
176. Dubach, D., Callender, S., and Moore, C. V., *Federation Proc.*, **7**, 270 (1948)
177. Sols, A., and Ponz, F., *Rev. espan. fisiol.*, **3**, 207–11 (1947)
178. Penhos, J. C., *Rev. soc. argentina biol.*, **22**, 377–82 (1946); *Chem. Abstracts*, **41**(14), 4552 (1947)
179. Larralde, J., *Rev. espan. fisiol.*, **3**, 31–38 (1947)
180. Huidobro, F., Valdés, R., and Dávila, M., *J. Pharmacol. Exptl. Therap.*, **92**, 336–44 (1948)
181. Martini, V., *Boll. soc. ital. biol. sper.*, **23**, 306 (1947); *Chem. Abstracts*, **42**(2), 674 (1948)
182. Basu, N. M., and Ray, G. K., *Indian J. Physiol. Allied Sciences*, **1**, 17–26 (1947); *Biol. Abstracts*, **22**(1), 580 (1948)
183. Campbell, P. N., and Dawson, H., *Biochem. J.*, **41**, xl (1947)
184. Dent, C. E., and Schilling, J. A., *Biochem. J.*, **42**, xxix-xxx (1948)
185. Hess, W. C., *Federation Proc.*, **7**, 159–60 (1948)
186. Frazer, A. C., *Chemistry & Industry*, (27), 379–82 (1947); *Nutrition Abstracts & Revs.*, **17**(3), 3360 (1948)
187. Frazer, A. C., *Brit. Med. J.*, **2**, 641–45 (1947)

188. LUNDBAEK, K., AND MAALØE, O., *Acta Physiol. Scand.*, **13**, 247–52 (1947)
189. BLACK, D. A. K., BOUND, J. P., AND FOURMAN, L. P. R., *Quart. J. Med.*, **16**, 99–109 (1947)
190. BLACK, D. A. K., AND FOURMAN, L. P. R., *Brit. Med., J.*, **2**, 645–47 (1947)
191. COOKE, W. T., FRAZER, A. C., PEENEY, A. L. P., SAMMONS, H. G., AND THOMPSON, M. D., *Quart. J. Med.*, **17**, 9–24 (1948)
192. HOFFMAN, M. M., MASSON, G., AND DESBARATS, M. L., *Endocrinology*, **42**, 279–84 (1948)
193. HEERSMA, J. R., AND ANNEGERS, J. H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 339–41 (1948)
194. ZILVERSMIT, D. B., CHAIKOFF, I. L., AND ENTENMAN, C., *J. Biol. Chem.*, **172**, 637–50 (1948)
195. ARTOM, C., AND SWANSON, M. A., *Federation Proc.*, **7**, 144 (1948)
196. BOLLMAN, J. L., AND FLOCK, E. V., *Federation Proc.*, **7**, 269 (1948)
197. FLOCK, E. V., AND BOLLMAN, J. L., *Federation Proc.*, **7**, 154–55 (1948)
198. GROEN, J., *Am. J. Med.*, **4**, 814–26 (1948)
199. WALDRON, J. M., AND FRIEDMAN, M. H. F., *Rev. can. biol.*, **7**, 201 (1948)
200. RADICE, J. C., AND HERRAIZ, M. L., *Rev. assoc. méd. argentina*, **61**, 287–92 (1947); *Chem. Abstracts*, **41**(21), 6938 (1947)
201. LEONHARDI, G., *Z. ges. inn. Med.*, **2**, 376–84 (1947); *Chem. Abstracts*, **42**(10), 3473 (1948)
202. KREULA, M. S., *Biochem. J.*, **41**, 269–73 (1947)
203. SOBEL, A. E., SHERMAN, M., LICHTBLAU, J., SNOW, S., AND KRAMER, B., *J. Nutrition*, **35**, 225–38 (1948)
204. SOBEL, A. E., BESMAN, L., AND KRAMER, B., *Federation Proc.*, **7**, 189–90 (1948)
205. MAY, C. D., AND LOWE, C. U., *J. Clin. Invest.*, **27**, 226–30 (1948)
206. ALEXANDER, B., LORENZEN, E., HOFFMAN, R., AND GARFINKEL, A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 275–78 (1947)
207. STEWART, H. C., AND MAY, J. R., *Lancet*, **II**, 857 (1947)
208. ROSE, F. L., AND SPINKS, A., *British J. Pharmacology*, **2**, 65–78 (1947)
209. PONOMAREV, G. A., *Farmakol. i Toksikol.*, **10**, 16–20 (1947)
210. SÉQUIN, F., *Rev. can. biol.*, **6**, 724–28 (1947)
211. BASU, U. P., MUKHERJEE, S., AND BANERJEE, R. P., *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 266 (1947)
212. BURROWS, W., *Federation Proc.*, **7**, 302–3 (1948)
213. LIGON, E. W., MADDEN, R. A., DAVIS, P. L., AND SMITH, P. K., *Federation Proc.*, **7**, 240 (1948)
214. BERMAN, J. K., BROWN, H. M., FOSTER, R. T., AND GRISELL, T. L., *J. Am. Med. Assoc.*, **135**, 918–19 (1947)
215. COGSWELL, H. D., *Ann. Surgery*, **127**, 377–82 (1948)
216. EULER, C. v., AND SJÖSTRAND, T., *Acta Physiol. Scand.*, **14**, 363–72 (1947)
217. DOWNMAN, C. B. B., MCSWINEY, B. A., AND VASS, C. C. N., *J. Physiol. (London)*, **107**, 97–106 (1948)
218. THEOBALD, G. W., *Lancet*, **I**, 119 (1948)
219. GRIMSON, K. S., HESSER, F. H., AND KITCHIN, W. W., *Surgery*, **22**, 230–45 (1947)
220. HOLZMANN, E. M., AND SAKHAROVA, D. S., *Bull. biol. méd. exp. U.R.S.S.*, **23**, 116–19 (1947); *Brit. Chem. Abstracts*, **AIII**, 240 (1948)

221. GREGORY, R. A., *J. Physiol.* (*London*), **106**, 95–103 (1947)
222. BLAIR, H. A., DERN, R. J., AND BATES, P. L., *Am. J. Physiol.*, **149**, 689–701 (1947)
223. ALSTEAD, S., AND PATTERSON, J. F., *Lancet*, **I**, 437–39 (1948)
224. SCHWEINBURG, F., FRANK, E., SEGAL, A., AND FINE, J., *Proc. Soc. Exptl. Biol. Med.*, **66**, 45–46 (1947)
225. IVANOV, D. I., *Am. Rev. Soviet Med.*, **5**, 49–51 (1948)
226. GUEST, M. M., *Federation Proc.*, **7**, 46 (1948)
227. BERNHARD, K., AND BULLET, F., *Helv. Chim. Acta*, **30**, 1784–86 (1947); *Chem. Abstracts*, **42**(4), 1339 (1948)
228. PHILLIPSON, A. T., *J. Exptl. Biol.*, **23**, 346–49 (1947)
229. SHOSHKES, M., *Gastroenterology*, **9**, 765–72 (1947)
230. ANNEGERS, J. H., BOUTWELL, J. H., AND IVY, A. C., *Gastroenterology*, **10**, 486–95 (1948)
231. WOLLAEGER, E. E., COMFORT, M. W., AND OSTERBERG, A. E., *Gastroenterology*, **9**, 272–83 (1947)
232. DAVIS, R. E., AND IVY, A. C., *Federation Proc.*, **7**, 25–26 (1948)
233. COLE, F., BARONOFSKY, I. D., AND WANGENSTEEN, O. H., *Surgery*, **21**, 881 (1947)
234. DAMERON, J. T., AND WANGENSTEEN, O. H., *Gastroenterology*, **10**, 859–65 (1948)
235. LEVEEN, H. H., *Gastroenterology*, **8**, 648–61 (1947)
236. STERN, I. F., GROSSMAN, M. I., AND IVY, A. C., *Surgery*, **22**, 552–57 (1947)
237. STEINBERG, M. E., AND BRUNKOW, M. D., *Proc. Soc. Exptl. Biol. Med.*, **66**, 157–58 (1947)
238. CUMMINS, G. M., GROSSMAN, M. I., AND IVY, A. C., *Gastroenterology*, **10**, 714–26 (1948)
239. FRIESEN, S. R., STATE, D., JASPER, D. E., FINN, M., AND WANGENSTEEN, O. H., *Surgery*, **23**, 167–77 (1948)
240. LILLEHEI, C. W., AND WANGENSTEEN, O. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 129–31 (1948)
241. LILLEHEI, C. W., AND WANGENSTEEN, O. H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 49–52 (1948)
242. LILLEHEI, C. W., DIXON, J. L., AND WANGENSTEEN, O. H., *Proc. Soc. Exptl. Biol. Med.*, **68**, 125–28 (1948)
243. LEVEEN, H. H., *Surg. Gynecol. Obstet.*, **86**, 164–68 (1948)
244. BARONOFSKY, I. D., *Gastroenterology*, **10**, 301–4 (1948)
245. WINTER, C. A., AND MUSHETT, C. W., *Federation Proc.*, **7**, 136 (1948)
246. PRICE, P. B., *Surg. Gynecol. Obstet.*, **86**, 59–63 (1948)
247. PAULS, F., WICK, A. N., AND MACKAY, E. M., *Gastroenterology*, **8**, 774–82 (1947)
248. HARKINS, H. N., AND HOOKER, D. H., *Surgery*, **22**, 239–45 (1947)
249. PAULS, F., WICK, A. N., AND MACKAY, E. M., *Science*, **107**, 19–20 (1948)
250. DRYER, R. L., KATZ, J., PAUL, W. D., AND ROUTH, J. I., *Federation Proc.*, **7**, 152 (1948)
251. LITTLE, J. M., OOGLE, B. C., TEAGLEY, J. D., AND COYER, D., *Science*, **106**, 448–49 (1947)
252. RISLEY, E. A., RAYMOND, W. B., AND BARNES, R. H., *Am. J. Physiol.*, **150**, 754–59 (1947)

253. SALTZSTEIN, H. C., SANDWEISS, D. J., HAMMER, J. M., HILL, E. J., AND VANDENBERG, H. J., JR., *Arch. Surg.*, **55**, 125–29 (1947)
254. NASIO, J., *Rev. Gastroenterol. (N. Y.)*, **14**, 340–44 (1947)
255. NASIO, J., *Rev. Gastroenterol. (N. Y.)*, **14**, 467–78 (1947)
256. GRINDLAY, J. H., *Minnesota Med.*, **31**, 257–58 (1948)
257. HILSABECK, J. R., AND HILL, F. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 155–56 (1947)
258. DE MURO, P., AND FICARI, A., *Rev. Gastroenterol. (N. Y.)*, **14**, 860–68 (1947)
259. MEYER, K., PRUDDEN, J. F., LEHMAN, W. L., AND STEINBERG, A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 220–21 (1947)
260. HANRAHAN, E. M., *Bull. Johns Hopkins Hosp.*, **81**, 131–49 (1947)
261. VANZANT, F. R., *Gastroenterology*, **8**, 768–73 (1947)
262. OBERHELMAN, H. A., JR., AND DRAGSTEDT, L. R., *Proc. Soc. Exptl. Biol. Med.*, **67**, 336–39 (1948)
263. WOODWARD, E. R., DRAGSTEDT, L. R., TOVEE, E. B., OBERHELMAN, H. A., JR., AND NEAL, W. B., JR., *Proc. Soc. Exptl. Biol. Med.*, **67**, 350–51 (1948)
264. ROBERTSON, C. R., AND GROSSMAN, M. I., *Federation Proc.*, **7**, 103 (1948)
265. FELDMAN, M., AND MORRISON, S., *Gastroenterology*, **10**, 502–3 (1948)
266. HARKINS, H. N., HOOKER, D. H., ALFORD, T. C., JR., AND CALLANDER, J. *Bull. Johns Hopkins Hosp.*, **81**, 79 (1947)
267. OLIVER, J. V., *Arch. Surgery*, **55**, 180–88 (1947)
268. SALTZSTEIN, H. C., SANDWEISS, D. J., HAMMER, J. M., HILL, E. J., AND VANDENBERG, H. J., JR., *Arch. Surgery*, **55**, 130–40 (1947)
269. SNAPE, W. J., *Gastroenterology*, **10**, 129–34 (1948)
270. SNAPE, W. J., FRIEDMAN, M. H. F., AND THOMAS, J. E., *Gastroenterology*, **10**, 496–501 (1948)
271. DUGAL, L. P., LEBLOND, C. P., AND THÉRIEN, M., *Can. J. Research*, **23**[E], 244–58 (1945)
272. QUIGLEY, J. P., JOHNSON, V., AND SOLOMON, E. I., *Am. J. Physiol.*, **90**, 89–98 (1929)
273. VISSCHER, M. B., *Federation Proc.*, **1**, 246–55 (1942)
274. BULL, H. B., AND GRAY, J. S., *Gastroenterology*, **4**, 175–82 (1945)
275. DAVENPORT, H. W., AND FISHER, R. B., *Am. J. Physiol.*, **131**, 165–75 (1940)
276. FRIEDMAN, M. F. H., AND SANDWEISS, D. J., *Am. J. Digestive Diseases*, **13**, 108–13 (1946)
277. BARRINGTON, E. J. W., *J. Physiol.*, **100**, 80–93 (1941)
278. AMBACHE, N., *J. Physiol.*, **104**, 266–87 (1946)
279. HAHN, P. F., BALE, W. F., AND WHIPPLE, G. H., *Proc. Soc. Exptl. Biol. Med.*, **61**, 405–6 (1946)
280. SHAY, H., KOMAROV, S. A., SIPLET, H., AND GRUENSTEIN, M., *Am. J. Digestive Diseases*, **14**, 99–104 (1947)

VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM[1]

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In the selection of articles to be reviewed under this heading consideration has been given to the fact that some of the visceral functions of the nervous system are discussed in sections on physiological effects of heat and cold, respiration, digestive system, liver, peripheral circulation, heart, kidney, reproduction, pharmacology, and others.

The nomenclature of visceral neurophysiology continues to become more confused. Many older terms are outgrowths of early misconceptions, and some newer terms frequently are not used in the sense originally assigned to them. Standardization of terminology by an interested group of physiologists, pharmacologists, and anatomists should be attempted. Further breakdown of early broad generalizations about the physiology of the two major divisions of the autonomic nervous system is apparent, since exceptions to most of these generalizations continue to accumulate.

The new book by Pi Suner (1) is one of the most extensive works available dealing primarily with the physiology of the autonomic nervous system. Bacq (2) has reviewed the literature concerning chemical transmission of nerve impulses in invertebrates. Responses to acetylcholine and to cholinesterases indicate the presence of cholinergic nerves in some invertebrates, e.g., annelids, and absence of cholinergic nerves in other invertebrates, e.g., most arthropods and mollusks. Existence of adrenergic nerves is considered probable in annelids; but, in general, effector cells of invertebrates are relatively unresponsive to epinephrine. In a review by Van Campenhout (3) an attempt is made to classify various structures which are characterized by an intimate association of epithelial cells and neural elements. These are designated "epithelioneural" bodies and are divided into neuroectodermal organs, neuroentoblastic organs, neuromesoblastic organs, and neuroepithelial associations of doubtful origin.

[1] This review covers the period from July, 1946 to June, 1948.

Physiological Anatomy

Developmental anatomy and growth.—Yntema & Hammond have studied depletions in the thoracolumbar system following removal of the occipital, cervical (4), thoracic, and lumbar (5) portions of the neural crest. They conclude that cervical sympathetic ganglion cells arise from local neural crest, the rudiments of the superior cervical ganglion lying in the neural crest at occipital and upper cervical levels. Establishment of postcarotid and paravertebral trunks is dependent upon the presence of neural crest. The preganglionic column and its fibers differentiate in the absence of the neural crest and of sympathetic ganglia. Peripheral sympathetic neurons in the thoracic and lumbar region and the chromaffin cells of the adrenal medulla arise from the neural crest. On the other hand, enteric plexuses and Remak's ganglion are not obviously affected by removal of the thoracic and upper lumbosacral portions of the neural crest. The reader can refer to Kuntz's discussion of histogenetic relationships (6) for a different viewpoint and for a critical discussion of this controversial subject. The major question in this type of study is whether or not the extirpations have involved structures in addition to the neural crest.

Murray & Stout (7) have found that adult human sympathetic ganglion cells can survive in lying-drop culture for a period of several months. During this period many ganglion cells migrate away from the explant for a distance of a few millimeters, and some of these undergo mitotic division. In experiments by Kuntz & Sulkin (8, 9) amitotic division of neuroglial cells has been observed in autonomic ganglia from man and from cats and dogs; and hyperplasia of the interstitial tissue, including the capsule cells, has been induced in experimental animals by prolonged faradic stimulation of the preganglionic fibers.

Innervation of the smooth muscle of the eye and of the eyelids.—Sunderland & Hughes (10) have made an anatomical study of the ocular nerves in man with particular reference to the pupilloconstrictor pathway. According to Kuntz & Richins (11) parasympathetic denervation of the eye in cats and dogs produces marked but not maximal dilatation of the pupil and abolishes the pupillary dilatation in response to peripheral painful stimuli. Evidence is presented to support the view that adrenergic fibers pass from the ciliary ganglion to exert an inhibitory action on the circular muscle

of the pupil. Results of studies on the same laboratory (12), using cats under sodium pentobarbital anesthesia, seem to indicate that the reflex inhibition of the ciliary muscle that is produced by peripheral painful stimuli likewise involves conduction of impulses from the ciliary ganglion to the ciliary muscle through inhibitory adrenergic components of the ciliary nerve. Isola & Bacq (13) find that the smooth muscle in the lower eyelid of the cat and dog is considerably stronger than that of the upper eyelid. This muscle has an excitatory adrenergic innervation coming from the superior cervical ganglion, and its response to autonomic drugs resembles the responses of the smooth muscle of the upper eyelid and the nictitating membrane.

Innervation of cutaneous areas.—Richter (14) has studied the cutaneous areas affected by upper thoracic and stellate ganglionectomies by means of the electrical skin resistance method. Successful denervation of the hand appears to depend largely on removal of the second thoracic ganglion. In most instances the central part of the face is affected little or not at all. A similar characteristic pattern of low resistance (residual "sympathetic activity") on the face has been noted by Ray & Console (15) following removal of the sympathetic chain from the stellate ganglion to the second lumbar ganglion. Results of each of these two studies indicate that the face receives part of its sudomotor innervation from some level above the stellate ganglion. In the latter study (15) it is shown also that dermatomes Th8-L3 receive part of their sudomotor innervation through pathways that are not destroyed by removal of the sympathetic chains from the stellate ganglion to L2 or 3. This residual innervation to the Th12 to L2 or 3 area is destroyed by spinal anesthesia or by sectioning the corresponding anterior roots, the first lumbar root being the most important. On the basis of evidence that the pathway can be blocked by tetraethylammonium chloride it is considered that the usual pre- and postganglionic fibers must be present, and it is suggested that the ganglia may be in the plexus about the aorta, or behind the psoas muscle, or in the lumbar nerves themselves.

Innervation of the heart.—Stotler & McMahon (16) have studied morphological details of the conducting system and innervation of the human heart. The sinoatrial node and the atrioventricular node receive a rich nerve supply, and the atrioventricular bundle and proximal third of the bundle branches are found to be

well supplied with nerves. They believe that the motor innervation of the heart is confined to elements of the conducting system which intervene between nerves and cardiac muscle. A subendocardial plexus, presumed to be sensory in function, is described.

Pannier (17), using cats and dogs anesthetized with morphine and chloralose, has traced cardioaccelerator pathways by direct stimulation with faradic current. In addition to the well-known sympathetic cardioaccelerator pathways, he states that cardio accelerator pathways in the vagus nerve were demonstrated in 80 per cent of the dogs studied. Vagal cardioaccelerators come directly from the medulla, i.e., follow the same course as vagal cardio-inhibitory fibers. In the cat the superior cervical sympathetic ganglion and the upper portion of the vagus trunk does not contain cardioaccelerator fibers; but cardioaccelerator fibers, coming from the middle cervical sympathetic ganglion, join the vagus trunk by means of anastomotic branches. The reader can refer to Volume X of this series for other recent studies emphasizing the importance of vagal cardioaccelerator fibers in dogs.

In dogs under sodium pentobarbital Saccomanno, Utterback & Klemme (18) have studied effects on heart rate and blood pressure produced by stimulation of peripheral ends of sectioned spinal nerves. Stimulation of the eighth cervical and first thoracic nerves failed to produce perceptible effect. The weakest effective stimulation of the second and third thoracic nerves elicited a very marked rise in blood pressure and acceleration of heart rate. Stimulation of the fourth, fifth, and sixth thoracic nerves resulted in progressively diminishing effects on heart rate but caused elevation of blood pressure. Lindgren & Olivecrona (19) and White & Bland (20) have reported results of various operations for relief of angina pectoris. Over three hundred cases have been studied in these two series.

Microanatomical studies.—Kuntz & Richins (21) have cut various nerves to salivary glands in cats and rats and have stained the degenerating nerves by means of an activated protargol technique. They conclude that, contrary to current physiologic teaching, sympathetic nerves in salivary glands supply mainly blood vessels, while innervation of glandular elements is mainly or exclusively parasympathetic. Actually, it is also questionable whether there are any physiologic experiments which demonstrate that secretory fibers are supplied to salivary glands by the thoracolumbar

system. By similar methods, Kuntz & Morris (22) have studied the components and distribution of the spermatic nerves and nerves of the vas deferens. Blood vessels of the testis receive sympathetic innervation and appear to be devoid of parasympathetic innervation. They fail to find any innervation of interstitial cells of the testis. Innervation of the epididymis and the vas deferens is described in detail. In twelve male patients with paraplegia the most marked relaxing effect on the detrusor muscle of the urinary bladder was produced by bilateral block of S3 (23), and less effects were obtained from block of S2 or S4.

Fox *et al.* (24) state that nerve fibers arise from the periventricular region and pass to the ependyma of the third ventricle where they have endings that resemble those found in the carotid sinus and carotid body, and it is suggested that these endings may be sensitive to changes in blood pressure or blood constituents. Tsuker (25), confirming others, has found that extirpation of the superior cervical ganglion results in degeneration of most, but not all, of the nerve fibers to the choroid plexus.

Afferent fibers in the phrenic nerve.—Gernandt (26) has taken oscillographic records from the peripheral end of the sectioned phrenic nerve in cats and dogs under chloralose anesthesia during application of various noxious stimuli to the diaphragm. It is concluded that pain is transmitted in the phrenic nerve by delta and C fibers only. Kohrman, Nolasco & Wiggers (27) have stimulated the central end of the phrenic nerve cut low in the thorax in dogs under morphine and sodium barbital. Arterial pressures, respiration, and, in some cases, kidney volume, and right atrial pressure were recorded. The results indicate that afferent fibers of the phrenic nerve communicate with respiratory, cardio-accelerator and vasomotor centers. Current strength and frequency of stimulation determine whether pressor or depressor reactions are obtained.

Innervation of the small intestine.—There have been several new studies concerning afferent innervation of the small intestine and reflexes elicited by activation of afferent pathways from the intestine. In oscillographic studies utilizing cats under chloralose, Gernandt & Zotterman (28) have found that large afferent spike potentials occur in the splanchnic or mesenteric nerves, partly continuously and partly in volleys synchronously with the arterial pulse (beta group of class A fibers). Volleys synchronous with the pulse increase with a rise in blood pressure and seem to originate

from pacinian corpuscles between the two blades of the mesentery. These receptors can be excited by mechanical stimulation or by a puff of air over the mesentery. Injurious stimuli applied to the intestinal wall produce impulses in delta fibers and in C fibers. Passing of a strong peristaltic wave was seen to produce a strong response from the small fibers and a low frequency response in a single large fiber from the loop being studied. Youmans & Folts found that impulses are produced in the nerves of the mesentery by intestinal distention (29); and Youmans (30) has discussed evidence that motor functions of the small intestine are under extrinsic nervous regulation through the intestino-intestinal inhibitory reflex which is initiated by changes in pressure within the intestinal lumen.

Responses of skeletal muscle and cardiovascular responses are produced by noxious stimuli applied to the small intestine (31). The former consist of contraction of abdominal muscles and various types of leg movements. The vascular response consists of a rise in blood pressure, and the vascular and somatic responses may be dissociated. The decerebrated-cordotomized animal, the cord being cut in the upper thoracic region, seems to be the most sensitive preparation. As indicated by elicitation of the above reflexes and of reflex pupillary dilatation (32) the intestine is sensitive to pinching, squeezing, cutting, scratching, 1.3 per cent potassium chloride, 0.1 *N* or 1 *N* hydrochloric acid or 10 per cent sodium chloride, and to heating to above 46°C. Moderate changes in temperature are ineffective. These visceromotor reflexes have been studied by von Euler & Sjöstrand (33) using cats under light barbiturate anesthesia or after decapitation.

Efferent impulses have been studied in the splanchnic nerve of the cat (34). These are sometimes continuous and sometimes synchronous with respiration or with heart beats. The rate of discharge of impulses is altered by various procedures which reflexly alter vasoconstrictor tonus, and this is true only when innervation of the carotid sinuses and aortic arch is intact. The number of impulses is increased by carbon dioxide accumulation both before and after sinoaortic denervation. The types of fibers in the hypogastric nerve have been studied by oscillographic methods (35).

Carotid sinus reflexes.—Wang & Borison (36) have compared vagal and sympathetic components of the carotid sinus cardiovascular reflexes in dogs anesthetized with sodium pentobarbital.

The slowing caused by vagal activation appears suddenly and disappears rapidly, while the slowing due to inhibition of cardio-accelerator nerves develops gradually and is more persistent. Disappearance of the sinovagal bradycardia is due in part to buffering action of the aortic-depressor nerve and in part to the phenomenon in the effector organ known as "vagal escape." They believe that sodium pentobarbital is a satisfactory anesthetic for studies of carotid sinus reflexes. However, vasoconstrictor compounds, such as pitressin and neosynephrine, produce mainly a rise in blood pressure and a relatively slight reflex cardiac slowing in dogs under sodium pentobarbital, while in unanesthetized dogs a similar dose of vasoconstrictor agent produces a lesser rise in blood pressure and severe bradycardia. This result indicates impaired sensitivity of the sinoaortic buffer reflexes. Some barbiturates also exert a partial blocking action at cholinergic neuro-effector junctions. Wang & Borison (37), using similar methods, have concluded that there is a small crossed component for the sinovagal reflex and a large crossed component for the vasomotor response to sinus pressure. The smallness of the crossed component of the sinovagal reflex is not evident from data presented. The much greater sustained slowing produced by distention of both sinuses than is produced by either alone (pressure in the other remaining constant) would seem to indicate a possibility of approximately 50 per cent crossing. It is known that unilateral carotid sinus pressure produces bilateral depression of cardio-accelerator tone (38). Also, the production of a slow nodal rhythm in some patients by pressure on the left carotid sinus would be difficult to explain in terms of a predominately uncrossed pathway.

Dorsal root vasodilators.—Further evidence has been obtained by means of chronaximetric and pharmacological studies that dorsal roots contain special vasodilator neurones having certain characteristics of sympathetic neurons (39).

Extraction and Identification of Epinephrine and of Adrenergic Neurohormones

Von Euler (40) has studied the sympathomimetic activity of extracts prepared from various nerves. The amount of sympathomimetic substance present in the extracts is expressed in epinephrine equivalents as measured on the blood pressure of the cat; however, on the basis of various chemical and biological tests, he

concludes that the substance resembles norepinephrine rather than epinephrine. Von Euler (40) infers that the active substance is the physiological transmitter of adrenergic nerve action; however, there are alternative possibilities. The significance of the high content of this sympathomimetic substance in sensory nerves of the skin is not clear, since these nerves have not been demonstrated to be adrenergic. Von Euler (41) has found that extracts of the spleen of cattle contain a depressor principle and a pressor principle; and the action of the pressor principle is enhanced by cocaine and blocked in part by ergotamine. These results and several color reactions are interpreted as indicating that the active substance is identical with or closely related to norepinephrine. A sympathomimetic substance bearing a closer resemblance to norepinephrine than to epinephrine also has been found in extracts made from heart muscle of several species (42) and in extracts of normal human and bovine blood (43). A preliminary report by von Euler (44) lists the amounts of acetylcholine, histamine, and *dl*-norepinephrine equivalents in various types of nerves; and he states that the presence of large amounts of histamine in certain sympathetic nerves suggests a specific role of this substance. All of these studies may be interpreted as being in accord with and lending support to the theory that so-called sympathin E is norepinephrine. Bacq (45) has prepared extracts of spleen by von Euler's method and has likewise obtained a sympathomimetic substance whose actions on the nictitating membrane and on the nonpregnant uterus of the cat are duplicated by norepinephrine. Bacq (45) believes that the idea of two sympathins may be reduced now to the simple notion of two sympathomimetic substances,—epinephrine and norepinephrine (corresponding to so-called sympathin I and sympathin E respectively). This possibility was one of several suggested by Bacq in 1935 (46) and carefully studied and supported by Greer *et al.* (47) in 1938. Gaddum & Goodwin (48) also have autoassayed on various organs the actions of the substance produced by stimulating hepatic nerves and have obtained results compatible with the theory that "liver sympathin" is norepinephrine rather than epinephrine. West (49) has developed chemical tests to differentiate epinephrine and norepinephrine, and he reports (50) that normal rabbit's blood contains an average epinephrine concentration of 0.098 μg. per ml. No norepinephrine was found in normal rabbit blood. It may be

recalled that others have failed to find measurable amounts of epinephrine in normal blood (51), and values for epinephrine in blood that are obtained by chemical methods tend to run higher than those obtained by bioassay. In the studies comparing the properties of sympathin and norepinephrine the *dl* form of the compound has been used, but it has been postulated that the compound occurs naturally in the laevo form. The *l*-norepinephrine is now available for the first time (52); and it is found to have a pressor potency approximately 60 per cent greater than that of *l*-epinephrine, whereas *d*-norepinephrine has a pressor potency only 3 to 4 per cent of that of *l*-epinephrine. Excised strips of ileum of the rabbit and guinea pig are relaxed by *l*-norepinephrine to about the same degree as by *l*-epinephrine, but the latter is thirty times as potent as the former in relaxing the nonpregnant rat uterus. The relatively high pressor potency of *l*-norepinephrine, as compared with *l*-epinephrine, is due, perhaps to the relatively low potency of *l*-norepinephrine as a dilator of arterioles having an inhibitory adrenergic innervation rather than to a potency greater than epinephrine in arterioles having an excitatory adrenergic innervation.

By various chemical and biological tests Raab & Humphreys (53) have shown that sympathetic ganglia contain relatively high concentrations of epinephrine and epinephrine-like compounds; The concentration in postganglionic fibers is somewhat lower and diminishes after severance of the fiber or during prolonged stimulation. The chromogenic material present in most sympathetically innervated tissues differs from epinephrine proper even in the case of its massive accumulation following epinephrine injection. These investigators suggest that epinephrine and related compounds may be formed in ganglion cells and flow down the axons under the influence of adequate stimuli. Total sympathectomy, combined with adrenal inactivation, is followed by a marked diminution of the epinephrine-like substances in the heart muscle, liver, and spleen of cats (54). Raab (55) reports that he has isolated a sympathomimetic amine in relatively large quantities from all parts of the human brain and from animal brains. This substance has chromogenic and pharmacodynamic properties in common with epinephrine and norepinephrine, but it differs from both of these in some respects. It has been designated "encephalin."

Youmans (30) has discussed the problem of the nature of sym-

pathin in a monograph on nervous and neurohumoral regulation of intestinal motility. It becomes increasingly unlikely that there is a sympathin E or sympathin I having the properties originally postulated by Cannon & Rosenblueth (56). However, sympathin from some sources differs from epinephrine. The following simple theory is favored in the light of present information. Epinephrine is the mediator produced under physiological conditions at all adrenergic nerve endings; sympathin entering the circulation from the effector cell is epinephrine or a mixture which consists of epinephrine and varying amounts of other similar physiologically active substances which are intermediaries in the production or destruction of epinephrine. Norepinephrine is most likely a component of sympathin, but it is probably not the mediator produced by the nerve ending. Norepinephrine is much less potent than epinephrine in various effectors having an excitatory adrenergic innervation (30), and it equals the potency of epinephrine as an inhibitor in intestinal smooth muscle (57) and in sympathetic ganglia (58, 59).

Liberation and Actions of Epinephrine

Liberation of epinephrine.—On the basis of cross circulation experiments in dogs Malméjac & Chardon (60) have concluded that liberation of epinephrine during moderate hypoxia produced by breathing 10 per cent oxygen in 90 per cent nitrogen, like the vasomotor and respiratory responses, is accomplished through reflexes from the carotid and aortic bodies. On the other hand, the center concerned with causing liberation of epinephrine may be excited directly by a more severe degree of hypoxia. According to Dumont (61) the transplanted adrenal of the dog discharges large quantities of epinephrine in response to ischemia. Bülbring, Burn & de Elío (62), working with blood-perfused adrenal glands of the dog, find that a fall in oxygen supply, whether produced by a lowered arterial saturation or by deficient circulation, leads to a rise in epinephrine output. According to them, during anoxia the loss of epinephrine from the gland exceeds the amount discharged by the vein. They report a potentiating effect of epinephrine in arterial blood upon the output of epinephrine in response to stimulation of the splanchnic nerve. This is, in a sense, a return to Cannon's concept that epinephrine promotes liberation of epinephrine. It now appears possible that, although epinephrine does not di-

rectly cause liberation of epinephrine, it may increase the discharge produced in response to stimulation of the (cholinergic) secretory nerves to the adrenal medulla. Several investigators recently have reported a sensitizing effect of one neurohormone upon the action of the other (63, 64). Of the three mechanisms for epinephrine liberation in response to hypoxia it would seem that only the sensitive carotid and aortic body reflex mechanism is of any great importance in the intact animal. Physostigmine produces striking changes in the cells of the adrenal medulla (65). These consist of an increased tendency to indirect division, nuclear gigantism, and some features of nuclear degeneration. The authors suggest that these changes may be related to the fact that the secretory innervation of the adrenal medulla is cholinergic and that physostigmine causes liberation of epinephrine.

Effects of epinephrine on transmission in autonomic ganglia.—By two quite different methods, it has been demonstrated that physiological concentrations of epinephrine influence synaptic transmission in sympathetic ganglia (66 to 69). According to Marrazzi & Marrazzi (69) the initial action of epinephrine is inhibitory, and it is stated that this cannot be due to sensitization of the ganglion cells to acetylcholine, to the extent of causing block, since increasing the preganglionic stimulation causes excitation to break through the inhibition (66). A postinhibitory facilitation is described and is interpreted as a secondary event (69). Under the conditions of her experiments, Bülbring (68) observed a facilitating effect of small amounts of epinephrine and an inhibitory effect of larger amounts.

Metabolic effects of epinephrine.—Clement (70) has concluded that the sympathetic nervous system plays an important role in mobilization of fat from fat reserves following injection of extracts of anterior or posterior pituitary. It is further demonstrated that liberation of fat by hypophyseal hormones is not by an action at the site of the fat depot but indirectly through the nervous system (71). This conclusion is based on experiments with rats having the sympathetic nervous system destroyed unilaterally.

Leimdorfer, Arana & Hack (72) have reported a rapid and high rise in blood sugar after intracisternal injections of epinephrine while similar doses produce a slow mild rise after the intraperitoneal injection and no rise following intra-articular injection. No effects of epinephrine on the circulatory system are seen during

the rise in blood sugar produced by the intracisternal injections. They conclude that epinephrine does not readily pass out of the cerebrospinal fluid and that it causes an increase in blood sugar by acting directly on structures bathed by cerebrospinal fluid.

Repeated injections of epinephrine, in rats or cats, over a period of eight hours, causes considerable loss of sudanophilic material from the adrenal cortex (73). Various types of stress cause depletion of the lipids of the adrenal cortex whether the adrenal glands are innervated or denervated. Adrenal denervation prevents in part the loss of cortical lipids produced by insulin injection in rats but not in cats, even though epinephrine depletion is produced by insulin in both species.

Autonomic Neuroeffector Transmission

Barium chloride suppresses the cardio-inhibitory effect of vagal stimulation in dogs (74). This salt may be given until the vagal effect is no longer obtained, and the block may be reverted in part by large doses of potassium chloride. The heart of the dog is also less sensitive to acetylcholine after injection of barium chloride (75). On the other hand, the excitatory effect of vagal stimulation upon pancreatic secretion is not prevented by barium chloride (76). In hyperthyroid rabbits, cats, and rats vagal stimulation has little or no inhibitory effect on heart rate, and sometimes produces only cardiac acceleration (77). The cardio-inhibitory effect of the vagus is restored in hyperthyroid animals by anticholinesterases. Isolated hearts of hyperthyroid cats and guinea pigs are relatively insensitive to the inhibitory action of acetylcholine.

On the basis of the assumption that cooling of the intestine abolishes acetylcholine synthesis in the intestine but leaves the muscle responsive, Ambache (78) has come to the conclusion that barium ions and potassium ions stimulate intestinal muscle indirectly through release of acetylcholine and that calcium ions inhibit release of acetylcholine. Minz & Plotka (79) likewise state that the action of potassium chloride and barium chloride upon isolated rabbit intestine depends upon cholinergic mechanisms. They suggest that epinephrine also may intervene *in vivo* in the synthesis of acetylcholine (80). However, Emmelin & Feldberg (81) have tested Ambache's theory that barium ions and potassium ions act on intestinal muscle through release of acetylcholine and have obtained no evidence to support the theory. They consider that

the results of their work and of Ambache's may be interpreted as in accord with previous views concerning sites of action of various ions and autonomic drugs. Rydin (82) has studied the effect of different temperatures on the response of isolated rabbit intestine to various drugs. It is suggested that an intensified response to some autonomic drugs at lowered temperatures is caused by a dissimilar resistance of different kinds of "receptor substances" in the effector cells.

Certain visceral effector cells tend to escape from the influence of a sustained concentration of neurohormone or from prolonged stimulation of the efferent nerve supply. This tendency is quite pronounced in intestinal smooth muscle (30, 83, 84). The mechanism of escape, like the mechanism of sensitization following denervation, remains unexplained.

Visceral Reflexes

The experiments of Neil, Redwood & Schweitzer (85) provide an object lesson in the importance of taking effects of the anesthetic agent into consideration when interpreting results of studies involving visceral reflexes. They report that stimulation of the carotid sinus nerve in cats, decerebrated or under sodium pentobarbital anesthesia, produces the usually expected fall in blood pressure. Subsequent intravenous injection of chloralose converts the depressor response to a given stimulus into a marked pressor response. Cats which have received no drug other than chloralose (0.08 to 0.1 gm. per kg.) show a pressor response to stimulation of the carotid sinus nerve. Binet & Burstein (86) find, as would be predicted, that systemic administration of epinephrine produces reflex dilatation in peripheral vessels. The vasodilation is accomplished by means of reciprocal effects on vasodilator and vasoconstrictor tonus and is greatly diminished after vagotomy and denervation of the carotid sinuses. Also, during the hypertension produced by centripetal excitation of somatic nerves, there is a dilatation of the vessels of the perfused paw (87).

According to Hollinshead (88) the abdominal epitheliod bodies of the mouse and rat function as accessory chemoreceptors and are concerned primarily with vascular reflexes. The interpretations are based on observing responses to inhalation of nitrogen, or intravenous injection of cyanide, or local application of cyanide before and after section of the abdominal vagus and splanchnic

nerves. In studies with rabbits anesthetized with urethane Conklin (89) finds that after elimination of the carotid and aortic receptors and splanchnic nerves the pumping action of respiration is the chief factor promoting venous return when the animal is tipped to the head-up position.

Vasoconstriction occurs in the finger after deep inspiration (90). This is considered to be a reflex, but the location of the receptors concerned has not been determined. Malinow, Katz & Kondo (91) report that pulmonary emboli produce electrocardiographic changes in bilaterally vagotomized dogs, and these changes are similar to those produced by the same procedure in dogs having the vagi intact. Injection of starch into the pulmonary artery causes rapid breathing, but does not cause a significant change in activity of individual vagal nerve fibers (92). It is suggested that fibers arising from endings on the walls of blood vessels may be involved. Bageant & Raper (93) have reported that stellate block in two patients with pulmonary emboli gave dramatic and almost immediate relief from both pain and respiratory distress. Bilateral vagotomy in the rat, according to Reichsman (94), predisposes to pulmonary edema by producing inspiratory obstruction rather than by disturbance of vasomotor control of lung vessels.

Increased pressure in perfused pulmonary vessels in cats under urethane anesthesia causes a fall in systemic blood pressure and, in most cases, a decrease in heart rate (95), and the effect is abolished by ipsilateral vagotomy. Such a reflex, in conjunction with sinoaortic reflexes, would serve to maintain the proper distribution of blood between the pulmonary and systemic circuits and would protect the pulmonary circuit from pressures predisposing to pulmonary edema. Parin (95) postulates that the receptors for the reflex are on the arterial side. A similar reflex was studied by deBurgh Daly *et al.* (96), who assumed that it originated from sensory endings in the pulmonary vein.

It has been concluded that sensitization of the heart to epinephrine by cyclopropane anesthesia in dogs is on a reflex basis (97). The receptors concerned are located, for the most part, in the peripheral three centimeters of mesentery. Afferent pathways pass through the coeliac and superior mesenteric plexuses, splanchnics, and spinal cord to a brain center above the pons; and efferent impulses pass by way of the cardiac sympathetics. Sensitization

of the heart to epinephrine occurs in dogs under cyclopropane whether the adrenal glands are present or absent. However, endogenous epinephrine contributes to the production of the irregularities in cardiac rhythm seen in cats under cyclopropane anesthesia (98).

Guttmann & Whitteridge (99) have studied reflexes elicited by distention of the urinary bladder in patients with complete lesions of the spinal cord. When the lesion is at or below T6, distention of the bladder causes vasoconstriction in the toes, a slight rise in blood pressure, and vasodilatation in the fingers. When the lesion is at or above T5, bladder distention causes vasoconstriction in the fingers and the toes, a very large rise in blood pressure, a marked decrease in pulse rate and commonly ventricular beats, and a remarkable vasodilation in the neck, face, and nasal mucosa. Sweating also represents an outstanding component in the symptomatology elicited by bladder distention in these patients with complete cord lesions.

Central Levels of Function

Medulla oblongata.—Alexander (100) has stimulated the pressor and depressor regions in the medulla of the cat by means of the Horsley-Clark stereotaxic instrument. The pressor center lies anteriorly and laterally in the reticular formation of the medulla and the depressor center has a more medial and posterior position. Transections designed to remove a portion of the pressor region produce a reduction in blood pressure and in cardio-accelerator tone. The depressor center tonically inhibits the activity of the spinal cardiovascular centers. Hermann, Cier & Vial (101) have given further attention to the fact that the blood pressure is maintained in dogs under chloralose with the spinal cord transected at C 1. They state that maintenance of blood pressure is not caused by irritation of centrifugal vasoconstrictor pathways, since there is no fall in pressure following anesthetization with cocaine at the site of the transection.

In an hypoxic animal return to oxygen produces a sharp fall in blood pressure and an increased volume of the perfused paw (102). This response is attributed to removal of the reflex drive of the vasoconstrictor center from chemoreceptors. If so, the mechanism is analogous to that involved in the production of apnea on return

to oxygen in hypoxic animals. Further evidence has been obtained for the direct stimulant action of carbon dioxide on the vasoconstrictor center (103).

Hypothalamus.—Gellhorn, Cortell & Murphy (104) have demonstrated that activation of parts of the sympathetic system can be produced by stimulation of various parts of the spinal cord, medulla oblongata, or hypothalamus of cats. The hyperglycemic response to hypoxia and to injected epinephrine is present for several days after hypophysectomy, but disappears in the course of several weeks following hypophysectomy even though the fasting blood sugar is not significantly altered (105).

Brobeck (106) states that the obesity of animals with hypothalamic lesions is caused primarily by a marked increase in food consumption. There may be also a decrease in locomotor activity and a transitory decrease in basal heat production, but neither of these changes plays a constant, essential role in the production of obesity. Studies of the effect of vagotomy on appetite and on the development of obesity in animals with hypothalamic lesions have given inconclusive results (107). Mossberger (108) has reported the case of a five-day-old infant with a perforated duodenal ulcer and a hamartomatous growth of the tuberal region of the hypothalamus.

According to Uvnäs (109) the response of the urinary bladder to hypothalamic stimulation is greatly influenced by the frequency of the stimulus used. Inhibition or contraction is obtained from points scattered throughout the whole preoptic and hypothalamic area, but points giving bladder contraction seem to be concentrated in the rostral parts of the diencephalon.

Release of luteinizing hormone from the anterior lobe of the hypophysis is not induced by stimulation of the cervical sympathetic nerves or by stimulation of vagal afferents (110). On the other hand, bipolar stimulation of the hypothalamus, but not of the hypophysis, induced ovulation in three out of four rabbits. The authors believe that the hypothalamus, by an adrenergic humoral link, plays a major role in the release of luteinizing hormone from the anterior lobe of the hypophysis. In subsequent experiments (111) they found that, dibenamine, an agent that blocks the action of epinephrine on some effector cells, prevents ovulation if given intravenously within one minute after copulation but is ineffective if injection is delayed three minutes or more after coitus.

Harris (112) has found that stimulation of the supraoptico-hypophyseal tract in unanesthetized rabbits is effective in inhibiting water diuresis and in producing chloruretic and oxytocic actions; on the other hand, stimulation of the paraventricular and ventromedian hypothalamic nuclei does not cause secretory activity of the neurohypophysis. He summarizes evidence that the neurohypophysis is an endocrine gland concerned with regulation of certain renal and uterine functions. The anatomy of the nervous and vascular connections between the neurohypophysis and adenohypophysis has been studied in several species, and the results lend support to the view that the central nervous system regulates the activity of the adenohypophysis by means of a humoral relay through the hypophyseal portal vessels (113, 114). Thus it appears that the hypothalamus is concerned with control of both the posterior and anterior lobes of the pituitary gland. Secretory cells in the posterior lobe are probably directly innervated by the supraoptico-hypophyseal tract, while control of the anterior lobe is exerted probably by means of a humoral link (115).

Complete bilateral transection of the hypothalamus in rats interferes with the normal regulation of sleep (116). Structures in the caudal hypothalamic region and in the adjacent part of the midbrain tegmentum are important in maintaining the waking state, and there is evidence that a structure in the preoptic region is of specific importance for the capacity of sleeping. Evidence is offered that sleep is caused by an inhibitory action of the sleep center on the waking center. The hypothalamic centers involved in the regulation of sleep are topographically identical with those determining the autonomic balance.

Cerebral cortex.—Ward & McCulloch (117) have recorded electrical activity in hypothalamic nuclei following local application of strychnine sulfate to various areas of the cerebral cortex. They find discrete projections from area 6a of the cortex to the mammillary nuclei, the lateral hypothalamic area, and to the posterior hypothalamic area. Projections have been demonstrated to the supraoptic and paraventricular nuclei from specific areas of the frontal lobe and the orbital surface. Pupillary dilatation produced by electrical stimulation of area 8 of the cerebral cortex is abolished by section of the cervical sympathetic chain (118). This active dilator pathway involves the hypothalamus, but it is stated that the corticohypothalamic pathway is not a direct one. A mini-

mal pupillary dilatation, on the basis of inhibition of the oculomotor nucleus, is obtainable only under special conditions of anesthesia. Electrical stimulation of the orbital surface of the frontal lobe in the dog and monkey causes changes in blood pressure, respiration, and temperature of the extremities (119). A rise or a fall in blood pressure may be produced, and respiration may be arrested at any phase of the respiratory cycle. The temperature of the extremities is elevated 6° to 8°F. after chronic ablation of the posterior orbital gyrus in the monkey (119). Kremer (120) has compared the effects on blood pressure of electrical stimulation of the cortex and of local application of acetyl-β-methylcholine. This drug produced a fall in arterial blood pressure of 30 to 50 mm. Hg with a latency of 40 sec. when applied to an area in the motor cortex and another in the anterior ectosylvian gyrus of the dog. Since the effect on blood pressure observed is the same as that produced by the direct vasodilator action of acetyl-β-methylcholine and in view of the considerable latent period one must suspect that some part of this response, at least in some instances, is not due to cortical stimulation but to systemic distribution of the drug.

After frontal lobectomy in deeply anesthetized cats the blood sugar, pulse rate, and respiratory rate immediately rise (121). These changes are considered to be part of the mechanism which, in the unanesthetized animal, manifests itself as sham rage. Rinkel and co-workers (122) have studied the effects of carotid sinus stimulation and of a test dose of epinephrine in a series of patients before and after prefrontal lobotomy. A striking increase in the pressor response to epinephrine is observed after prefrontal lobotomy. It is considered that this result is not due to impaired buffer reflexes since the response to carotid sinus pressure is, if anything, increased after prefrontal lobotomy.

Kennard (123) has reviewed the anatomical and physiological evidence for interconnections between the autonomic system and the somatic motor system. The interrelations between these systems have been demonstrated at many levels from the neuroeffector junction to the cerebral cortex.

LITERATURE CITED

1. Pi Suner, A., *Sistema Neurovegetativo*, 817 pp. (Union Typographica Editorial Hispano-americana, Mexico, 1947)
2. Bacq, Z. M., *Biol. Rev. Cambridge Phil. Soc.*, **22**, 73–91 (1947)

3. VAN CAMPENHOUT, E., *Quart. Rev. Biol.*, **21**, 327–47 (1946)
4. YNTEMA, C. L., AND HAMMOND, W. S., *J. Exptl. Zoöl.*, **100**, 237–63 (1945)
5. HAMMOND, W. S., AND YNTEMA, C. L., *J. Comp. Neurol.*, **86**, 237–65 (1947)
6. KUNTZ, A., *The Autonomic Nervous System*, 687 pp. (Lea & Febiger, Phila., Penn., 1945)
7. MURRAY, M. R., AND STOUT, A. P., *Am. J. Anat.*, **80**, 225–73 (1947)
8. KUNTZ, A., AND SULKIN, N. M., *J. Comp. Neurol.*, **86**, 467–77 (1947)
9. KUNTZ, A., AND SULKIN, N. M., *J. Neuropathol. Exptl. Neurol.*, **6**, 323–32 (1947)
10. SUNDERLAND, S., AND HUGHES, E. S. R., *Brain*, **69**, 301–9 (1946)
11. KUNTZ, A., AND RICHINS, C. A., *J. Neurophysiol.*, **9**, 1–7 (1946)
12. KUNTZ, A., RICHINS, C. A., AND CASEY, E. J., *J. Neurophysiol.*, **9**, 445–51 (1946)
13. ISOLA, W., AND BACQ, Z. M., *Compt. rend. soc. biol.*, **141**, 842–43 (1947)
14. RICHTER, C. P., *J. Neurosurg.*, **4**, 221–32 (1947)
15. RAY, B. S., AND CONSOLE, A. D., *J. Neurosurg.*, **5**, 23–50 (1948)
16. STOTLER, W. A., AND MCMAHON, R. A., *J. Comp. Neurol.*, **87**, 57–72 (1947)
17. PANNIER, R., *Arch. intern. pharmacodynamie*, **73**, 193–259 (1946)
18. SACCOMANNO, G., UTTERBACK, R. A., AND KLEMME, R. M., *Ann. Surg.*, **125**, 49–56 (1947)
19. LINDGREN, I., AND OLIVECRONA, H., *J. Neurosurg.*, **4**, 19–39 (1947)
20. WHITE, J. C., AND BLAND, E. F., *Medicine*, **27**, 1–42 (1948)
21. KUNTZ, A., AND RICHINS, C. A., *J. Comp. Neurol.*, **85**, 21–32 (1946)
22. KUNTZ, A., AND MORRIS, R. E., JR., *J. Comp. Neurol.*, **85**, 33–44 (1946)
23. HEIMBURGER, R. F., FREEMAN, L. W., AND WILDE, N. J., *J. Neurosurg.*, **5**, 154–64 (1948)
24. FOX, C. A., ZEIT, W., DESALVA, S., AND FISHER, R., *Anat. Record*, **100**, 135 (1948)
25. TSUKER, M., *Arch. Neurol. Psychiat.*, **58**, 474–83 (1947)
26. GERNANDT, B., *Acta Physiol. Scand.*, **12**, 254–60 (1946)
27. KOHRMAN, R. M., NOLASCO, J. B., AND WIGGERS, C. J., *Am. J. Physiol.*, **151**, 547–53 (1948)
28. GERNANDT, B., AND ZOTTERMAN, Y., *Acta Physiol. Scand.*, **12**, 56–72 (1946)
29. YOUMANS, W. B., AND FOLTS, L., *Federation Proc.*, **5**, 116–17 (1946)
30. YOUMANS, W. B., *Nervous and Neurohumoral Regulation of Intestinal Motility*, 150 pp. (Interscience Publishing Company, New York, 1949)
31. DOWNMAN, C. B. B., AND MCSWINEY, B. A., *J. Physiol. (London)*, **105**, 80–94 (1946)
32. DOWNMAN, C. B. B., MCSWINEY, B. A., AND VASS, C. C. N., *J. Physiol. (London)*, **107**, 97–106 (1948)
33. EULER, C. V., AND SJÖSTRAND, T., *Acta Physiol. Scand.*, **14**, 363–72 (1947)
34. GERNANDT, B., LILJESTRAND, G., AND ZOTTERMAN, Y., *Acta Physiol. Scand.*, **11**, 230–47 (1946)
35. GRUNDFEST, H., AND AMPIL, D., *Federation Proc.*, **7**, 46 (1948)
36. WANG, S. C., AND BORISON, H. L., *Am. J. Physiol.*, **150**, 712–21 (1947)
37. WANG, S. C., AND BORISON, H. L., *Am. J. Physiol.*, **150**, 722–28 (1947)
38. BRONK, D. W., FERGUSON, L. K., AND SOLANDT, D. Y., *Proc. Soc. Exptl. Biol. Med.*, **31**, 579–80 (1934)

39. CHAUCHARD, B., AND CHAUCHARD, P., *Arch. intern. physiol.*, **54**, 134–38 (1946)
40. EULER, U. S. v., *Acta Physiol. Scand.*, **12**, 73–97 (1946)
41. EULER, U. S. v., *Acta Physiol. Scand.*, **11**, 168–86 (1946)
42. EULER, U. S. v., *J. Physiol.* (*London*), **105**, 38–44 (1946)
43. EULER, U. S. v., AND SCHMITERLÖW, C. G., *Acta Physiol. Scand.* **13**, 1–8 (1947)
44. EULER, U. S. v., *J. Physiol.* (*London*), **107**, 10P (1948)
45. BACQ, Z. M., *Compt. rend. soc. biol.*, **141**, 537–38 (1947)
46. BACQ, Z. M., *Ergeb. Physiol.*, **37**, 82–185 (1935)
47. GREER, C. M., PINKSTON, J. O., BAXTER, J. H. JR., AND BRANNON, E. S., *J. Pharmacol. Exptl. Therap.*, **62**, 189–227 (1938)
48. GADDUM, J. H., AND GOODWIN, L. G., *J. Physiol.* (*London*), **105**, 357–69 (1947)
49. WEST, G. B., *J. Physiol.* (*London*), **106**, 418–25 (1947)
50. WEST, G. B., *J. Physiol.* (*London*), **106**, 426–30 (1947)
51. BAIN, W. A., GAUNT, W. E., AND SUFFOLK, S. F., *J. Physiol.* (*London*) **91**, 233–53 (1937)
52. TAINTER, M. L., TULLAR, B. F., AND LUDUENA, F. P., *Science* **107**, 39–40 (1948)
53. RAAB, W., AND HUMPHREYS, R. J., *Am. J. Physiol.*, **148**, 460–69 (1947)
54. RAAB, W., AND MAES, J. P., *Am. J. Physiol.*, **148**, 470–77 (1947)
55. RAAB, W., *Am. J. Physiol.*, **152**, 324–39 (1948)
56. CANNON, W. B., AND ROSENBLUETH, A., *Am. J. Physiol.*, **104**, 557–74 (1933)
57. YOUMANS, W. B., AUMANN, K. W., AND HANEY, H. F., *Am. J. Physiol.*, **126**, 237–46 (1939)
58. MARRAZZI, A. S., *Science*, **104**, 6–8 (1946)
59. MARRAZZI, A. S., AND MARRAZZI, R. N., *Science*, **106**, 520–21 (1947)
60. MALMÉJAC, J., AND CHARDON, G., *Compt. rend. soc. biol.*, **141**, 395–96 (1947)
61. DUMONT, J. *Compt. rend. soc. biol.*, **141**, 1282–83 (1947)
62. BÜLBRING, E., BURN, J. H., AND DE ELÍO, F. J., *J. Physiol.* (*London*) **107**, 222–32 (1948)
63. BURN, J. H., *Physiol. Revs.*, **25**, 377–94 (1945)
64. MCDOWALL, R. J. S., *J. Physiol.* (*London*), **106**, 1–7 (1947)
65. MOREL, J., GINESTE, P. J., AND DERUDDER, A., *Compt. rend. soc. biol.*, **141**, 1240–41 (1947)
66. MARRAZZI, A. S., *Am. J. Physiol.*, **127**, 738–44 (1939)
67. MARRAZZI, A. S., *J. Pharmacol. Exptl. Therap.* **65**, 395–404 (1939)
68. BÜLBRING, E., *J. Physiol.* (*London*), **103**, 55–67 (1944)
69. MARRAZZI, A. S., AND MARRAZZI, R. N., *J. Neurophysiol.* **10**, 167–78 (1947)
70. CLEMENT, G., *Compt. rend. soc. biol.*, **141**, 317–20 (1947)
71. CLEMENT, G., AND SCHAEFFER, G., *Compt. rend. soc. biol.*, **141**, 320–22 (1947)
72. LEIMDORFER, A., ARANA, R., AND HACK, M. H., *Am. J. Physiol.*, **150**, 588–95 (1947)
73. VOGT, M., *J. Physiol.* (*London*), **106**, 394–404 (1947)
74. BOULET, L., AND BOULET, M. A., *Compt. rend. soc. biol.*, **141**, 1226 (1947)
75. BOULET, L., AND BOULET, M. A., *Compt. rend. soc. biol.*, **141**, 1226–27 (1947)
76. BOULET, L., AND BOULET, M. A., *Compt. rend. soc. biol.*, **141**, 1232–33 (1947)

77. HOFFMANN, F., HOFFMANN, E. J., AND TALESNIK, J., *Am. J. Physiol.* **148,** 689–99 (1947)
78. AMBACHE, N., *J. Physiol.* (*London*), **104,** 266–87 (1946)
79. MINZ, B., AND PLOTKA, C., *Compt. rend. soc. biol.*, **141,** 215–16 (1947)
80. MINZ, B., AND PLOTKA, C., *Compt. rend. soc. biol.*, **141,** 108–10 (1947)
81. EMMELIN, N., AND FELDBERG, W., *J. Physiol.* (*London*), **106,** 482–502 (1947)
82. RYDIN, H., *Acta Physiol. Scand.*, **11,** 270–78 (1946)
83. DELL, P., AND METZ, B., *Compt. rend. soc. biol.*, **137,** 485–86 (1943)
84. DELL, P., AND METZ, B., *Arch. intern. physiol.*, **54,** 292–304 (1946)
85. NEIL, E., REDWOOD, C. R. M., AND SCHWEITZER, A., *J. Physiol.* (*London*), **107,** 8P (1948)
86. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **141,** 630–33 (1947)
87. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **141,** 727–29 (1947)
88. HOLLINSHEAD, W. H., *Am. J. Physiol.*, **147,** 654–60 (1946)
89. CONKLIN, R. E., *Am. J. Physiol.*, **147,** 661–68 (1946)
90. GILLIATT, R. W., *J. Physiol.* (*London*), **107,** 76–88 (1948)
91. MALINOW, M. R., KATZ, L. N., AND KONDO, B., *Am. Heart J.*, **31,** 702–10 (1946)
92. WALSH, E. G., *J. Physiol.* (*London*), **106,** 466–70 (1947)
93. BAGEANT, W. E., AND RAPER, L. A., *Anesthesiology*, **8,** 500–5 (1947)
94. REICHSMAN, F., *Am. Heart J.*, **31,** 590–616 (1946)
95. PARIN, V. V., *Am. J. Med. Sci.*, **214,** 167–75 (1947)
96. DEBURGH DALY, I., LUDANY, G., TODD, A., AND VERNEY, E. B., *Quart. J. Exptl. Physiol.*, **27,** 123–46 (1937)
97. STUTZMAN, J. W., MURPHY, Q., ALLEN, C. R., AND MEEK, W. J., *Anesthesiology*, **8,** 579–83 (1947)
98. PETTINGA, F. L., AND STUTZMAN, J. W., *Federation Proc.*, **7,** 93 (1948)
99. GUTTMANN, L., AND WHITTERIDGE, D., *Brain*, **70,** 361–404 (1947)
100. ALEXANDER, R. S., *J. Neurophysiol.*, **9,** 205–17 (1946)
101. HERMANN, H., CIER, J. F., AND VIAL, J., *Compt. rend. soc. biol.*, **141,** 827–28 (1947)
102. MALMEJAC, G., CHARDON, G., AND NEVERRE, G., *Compt. rend. soc. biol.*, **141,** 396–98 (1947)
103. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **141,** 488–90 (1947)
104. GELLHORN, E., CORTELL, R., AND MURPHY, J. P., *Am. J. Physiol.*, **146,** 376–85 (1946)
105. SAFFORD, H., WELLS, L., AND GELLHORN, E., *Am. J. Physiol.*, **146,** 386–88 (1946)
106. BROBECK, J. R., *Physiol. Revs.*, **26,** 541–59 (1946)
107. BROOKS, C. McC., LOCKWOOD, R. A., AND WIGGINS, M. L., *Am. J. Physiol.*, **147,** 735–41 (1946)
108. MOSSBERGER, J. I., *J. Neuropathol. Exptl. Neurol.*, **6,** 391–400 (1947)
109. UVNÄS, B., *Proc. Soc. Exptl. Biol. Med.*, **64,** 181–85 (1947)
110. MARKEE, J. E., SAWYER, C. H., AND HOLLINSHEAD, W. H., *Endocrinology*, **38,** 345–57 (1946)
111. SAWYER, C. H., MARKEE, J. E., AND HOLLINSHEAD, W. H., *Endocrinology*, **41,** 395–402 (1947)

112. HARRIS, G. W., *Trans. Roy. Soc. (London)*, [B] **232,** 385–441 (1947)
113. GREEN, J. D., AND HARRIS, G. W., *J. Endocrinol.*, **5,** 136–46 (1947)
114. HARRIS, G. W., *J. Anat.*, **81,** 343–51 (1947)
115. HARRIS, G. W., *Brit. Med. J.*, **1,** 339–42 (1948)
116. NAUTA, W. J. H., *J. Neurophysiol.*, **9,** 285–316 (1946)
117. WARD, A. A., JR., AND MCCULLOCH, W. S., *J. Neurophysiol.*, **10,** 309–14 (1947)
118. WARD, A. A., AND REED, H. L., *J. Neurophysiol.*, **9,** 329–35 (1946)
119. DELGADO, J. M. R., AND LIVINGSTON, R. B., *J. Neurophysiol.*, **11,** 39–54 (1948)
120. KREMER, W. F., *Am. J. Physiol.*, **152,** 314–23 (1948)
121. KENNARD, M. A., HAMPEL, C. W., AND WILLNER, M. D., *Am. J. Physiol.*, **149,** 246–53 (1947)
122. RINKEL, M., GREENBLATT, M., COON, G. P., AND SOLOMON, H. G., *Arch. Neurol. Psychiat.*, **58,** 570–81 (1947)
123. KENNARD, M. A., *Psychosomat. Med.*, **9,** 29–36 (1947)

SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM[1]

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"Imposed on the simplest monosynaptic arcs of the cord are hierarchies of more comprehensive arcs, homeostatic for more complicated changes" (47).

Cerebral Cortex

The highest of these arcs traverse the cerebral cortex in which, adjacent to the dual sites of reception of afferent impulses from peripheral receptors, are effector areas with both motor and suppressor functions (29, 45, 64, 85). A part of each effector area initiates mutable changes in the receptor-bearing region. Another part inaugurates more stereotyped movement, lacking such specific reference. Still another part is concerned with reducing the cortical reception of the involved and other afferent impulses (6, 23), and with relaxing the musculature, both in this receptive region of the body and elsewhere for, unlike those of the cerebellum (see below), the cerebral suppressor areas do not exhibit somatotopic localization in their activity. From this point of view, the dominance of the somatic effector cortex (precentral gyrus) can be explained simply by the fact that it lies adjacent to the only receiving area in which the entire body is represented.

A background of intrinsic activity is maintained within the cerebral cortex by circuits to and from the thalamus, which, since they subtend long arcs with the periphery, form figurative chords. Those involving the thalamic relay nuclei are influenced directly by afferent impulses from receptors and dominate the local receiving areas to which they project (8, 16). Those of intralaminar and reticular thalamic nuclei exert more generalized influences (31, 32). More complex subtending connections, traversing the basal ganglia, hypothalamus, and midbrain, evidently modify thalamic activity and so, indirectly, that of the cortex which depends upon it. Still longer connections traverse the cerebellum (27, 70) and

[1] This review covers the period from July, 1947 to July, 1948

are directed back again, via the thalamus, not only to effector cortical areas but to receiving regions as well (69).

In addition to local complexities of cerebral structure (3, 4, 35, 36, 45, 77), these interconnections subtending direct arcs from receptors to effectors, and maintaining interminable activity within their compass, thus distinguish the rostral portion of the central nervous system from the caudal, in which latter, receptor initiated activity is very largely dispersed in discharge to effectors, though even here (40, 41, 44) and, more remarkably, even in outlying ganglia (37), it may serve relatively prolonged activity.

Prefrontal Cortex

Interest continues to be centered around prefrontal lobotomy (18, 20, 25,) or lobectomy (62) for the relief of mental disorders, and now advocated also for the relief of intractable pain (17). Ancillary experimental studies have explored the orbital and medial aspects of the frontal lobe. Stimulation of the cingular gyrus causes autonomic responses, complex tonic movements and profound suppression, both of all types of movement and of cortical electrical activity (34, 80). Ablation of area 24 in monkeys results in loss of fear and in social indifference (80).

Excitation of the orbital surface of the frontal lobe causes respiratory arrest and autonomic alterations, including peripheral vasodilatation with rapid rise in skin temperature (15, 68). In monkeys, ablation of area 13 resulted in motor hyperactivity (21) and, following orbital leucotomy in man (65), extroversion, increased motor activity, and euphoria were more marked than after the standard operation. The value of the suggestion (65) that these symptoms are the consequence of severing the uncinate fasciculus, interconnecting the frontal and temporal lobes (53), rather than due to the interruption of frontothalamic circuits (19, 48, 49) may soon be determined, for both temporal lobotomy (56) and medial thalamotomy (74, 75) are now being undertaken in patients with mental disorders.

Effector Cortical Areas

Archicortex.—So-called olfactory regions of the forebrain exert a suppressor influence upon hypothalamic and midbrain mechanisms executively involved in the expression of anger (5). In the absence of all neocortex, their presence is responsible for placidity;

their removal, in addition or alone, predisposes the animal to rage behavior upon minimal and normally inadequate stimulation. This suppression may be exerted through the ventromedial hypothalamic nucleus, injury to which is similarly followed by behavioral changes in the direction of savagery (30).

Second somatic effector area.—A second motor cortex has been identified in the monkey, anterior to and overlapping the second somatic receiving area, and with representation of body parts inverse to that in area 4 (76). Lying on the buried wall of the frontoparietal operculum and the posterior portion of the insula, the face region is anterosuperior and the leg region posteroinferior. The arm region lies between and is largest. Movements, which can be elicited in the chronic absence of the first motor cortex, are contralateral and most readily involve apical parts. Typical seizures are provoked by excessive stimulation, but no lasting motor defects follow removal of this area.

Primary somatic effector area.—Excitation of the leg portion of the monkey's motor cortex, under conditions opposing intracortical conduction, disclosed focal points yielding responses of single muscles (12, 66). Extensors had greater representation than flexors and distal muscles more than proximal ones. The observed topographical localization of muscles is suggested to find its greatest expression in the Betz cells which are organized in fields composed of a focus and a fringe, the latter exhibiting overlap.

Electromyographic recording of responses to stimulating the motor cortex, under conditions favoring facilitation, supports the principle of multiplicity of muscular representation (7). Cortical foci consist of bands initiating simple patterns of motion, out of which more complex purposive movements may be composed. With minimal stimulation, reciprocal innervation of antagonistic muscles is exhibited; stronger stimulation favors cocontraction, fixing joints. Responses are modified by the presence of muscle tone (7).

Frequency of discharge, which enables neural units to vary the intensity of their influence, may also determine where and how this influence is exerted. Different cranial motor nuclei are excited from the face area of the motor cortex by altering the frequency of its stimulation (3). Stimulus frequency is an important factor also in eliciting autonomic responses from frontal areas in monkey and man (39).

In a case of unilateral agenesis of the sensorimotor cortex, with an almost complete absence of the pyramidal tract, as contrasted with the preservation of extrapyramidal structures, the patient was able to employ the contralateral axial and postural musculature in generalized and stereotyped acts (57). Signs of spasticity (see below) were minimal or absent, however, and in the distal parts of the affected extremities all movements of a type that should not be called discrete (78, 79) were lacking.

Temporal effector area.—Movements of the ipsilateral pinna spreading to the face and neck, with higher voltages, are evoked from the buried posterior portion of the middle temporal gyrus, adjacent to the auditory receiving area (76).

Occipital effector area.—Parts of area 17 and 19, adjacent to the visual receiving area, initiate conjugate movements of the eyeballs (13). In the monkey, stimulation of the dorsal, middle, and ventral portions of area 17 respectively caused deviation of the eyes in downward, horizontal, and upward directions toward the opposite side. Since the dorsal portion of area 17 receives impulses from the inferior visual field, and vice versa, this organization is obviously purposeful in serving to direct the eyeballs toward the source of retinal stimulation.

Corticifugal connections concerned with upward deviation pass to the rostral parts of the anterior corpus quadrigeminum and oculomotor nucleus, which move the eyeball upward and elevate the lid (13). Those for downward deviation reach the caudal portion of the tectum and nucleus, innervating the inferior rectus. The suppressor pathway from area 19 is directed to the bulbar reticular formation, like that from 4-s and 24 (46).

Cerebellum

It now appears that within the cerebellar cortex, as in that of the cerebrum, there coexists at the dual sites of reception of afferent projections, effector areas capable of facilitating or suppressing movement.

Effector areas.—Cerebellar suppressor areas are present in portions of the anterior and paramedian lobes (26, 54, 55, 71) to which afferent tactile impulses are conveyed. Unlike those of the cerebrum, they exert their influence predominantly upon that region of the body from which afferent impulses were derived. For, in the anterior lobe, suppression of movement of the tail, hind-

limb, forelimb, or face is evoked by stimulating sites arranged anteroposteriorly in the lingula, centralis, culmen, and simplex lobules respectively. Sites near the midline affect activity of proximal musculature and more lateral sites, that of distal musculature (55).

Cerebellar suppression, effective against both cortically and reflexly induced movement, and more easily elicited in the cat than in the monkey, is mediated by the fastigial nuclei and their connections with the suppressor, bulbar reticular formation (71). Ablation of the cerebellar suppressor areas augments spasticity resulting from cerebral lesions, as might be expected to a greater degree in the cat (38) than in the monkey (73). By appropriate rostral or caudal ablation of the monkey's anterior lobe, this increase in spasticity may be limited respectively to the lower or upper extremity (73).

Facilitation of cortically or reflexly induced movement is the predominant result of stimulating the somatic receiving-effector areas of the monkey's cerebellum (55, 72), and it exhibits all the somatotopic relations existing for suppression in the cat. Facilitation occurs following interruption of the superior peduncle, suggesting that this influence is exerted through brain stem mechanisms rather than through the cerebrum. In the dog and monkey, low or high frequency of cerebellar stimulation determines whether suppression or facilitation is elicited from the same effector point (55); pathways for the two are suggested thereafter to diverge and be mediated by different roof nuclei.

Cerebrocerebellar interrelations.—Evoked potential studies have determined that the receiving-effector areas of the cerebral and cerebellar cortices are closely interconnected (27, 69, 70). Thus, stimuli applied to the cerebral somatic region yield responses in the cerebellar somatic region and vice versa, considerable somatotopic localization being preserved in these circuits. Excitation of the cerebral auditory or visual region similarly yields responses in the cerebellar audiovisual region and vice versa. More generalized interconnections exist between cerebral associational areas and crus I and II of the cerebellar cortex.

With cerebellar relations thus being revealed, there remains to be undertaken an analysis of the nature of olivary contributions (10, 33) and those for proprioception, of which latter the cerebellum was once called the "head ganglion" (28).

Cerebellar lesions.—A study of the consequences of cerebellar lesions in the cat (11) and monkey (9) extends the earlier findings of others. Ablation of the flocculonodular lobe (vestibular receiving area) produced disturbances of equilibrium and posture. Truncal ataxia followed lesions of the nonvestibular part of the vermis (audiovisual receiving area) and was associated with tremor of the head. Removal of the ansoparamedian (associational) cortex gave only slight and transient symptoms. The classic cerebellar signs of dysmetria, ataxia, and ataxic tremor, during voluntary movement, were encountered after lesions of the cortex of the anterior and simplex lobes (somatic receiving-effector area), and of the dentate and interposed nuclei, which latter lesions were followed also by abnormalities of involuntary movement, including static tremor (see below). Symptoms were more severe, and compensation was slower and less complete, after lesions of the central nuclei than after injury limited to the cortex, parallelism being drawn with comparable lesions of the cerebral hemisphere.

Brain Stem

From work of the past fifteen years, it is clear that the brain stem, through outflows to endocrine and autonomic systems, is involved in the homeostasis of many of the basic processes of the body. There are growing indications that it plays an equivalently important role in regulating the activity of the remainder of the central nervous system, a rostral portion being concerned with that of the cerebral cortex and a more caudal part with that of the cord.

Consciousness and petit mal seizures.—In the initially local, violent discharge of an epileptic seizure (24, 59, 60, 61) the neural area involved is incapable of normal activity and becomes functionally paralyzed. During petit mal seizures, the sole manifestation of which may be a loss of conciousness, such incapacitating discharge is evidently occurring in that part of the brain which is most essential for consciousness (1, 61). Electroencephalographic records in petit mal are characterized by 3 per sec. spike and wave sequences appearing synchronously in midfrontal leads and rapidly involving large areas of both hemispheres, without evidence of intracortical or callosal spread.

The site of initial discharge has, therefore, been located in a part of the diencephalon or midbrain to which connections with

wide areas of both halves of the cortex, and particularly the frontal lobes, are immediately available (31, 32, 61). In substantiation, all the electroencephalographic features of clinical petit mal have been reproduced in cats by electrical stimulation of the medial intralaminar region and massa intermedia of the thalamus (31), a region which had earlier been shown to be of importance in controlling, probably through intrathalamic circuits, the electrical activity of large cortical areas. The relation of this intralaminar thalamic system to consciousness is not immediately apparent though it is, of course, situated in close proximity to hypothalamic and midbrain structures, injury to which is followed by somnolence (63) or coma (42).

Tremor.—From the structurally undifferentiated core of the brain stem, a collection of reticulospinal paths descends into the cord, outside the pyramids, as the extrapyramidal system. This system is under the control of both the cerebrum and cerebellum and its impaired function results, among other things, in involuntary motion and in spasticity.

In monkeys, a tremor at rest, alternating in antagonistic muscles, follows injury to the tegmentum of the upper brain stem (82). This tremor, which appeared identical with that of Parkinson's disease in man, returned with motor power after lesions of cortical areas 4 and 6 [see also (14, 52)] and was unaffected by interrupting recurrent pallidal connections to the cortex. Records of electrical activity of the cerebral cortex and electromyograms of tremor showed no correlation, and the rhythm is attributed to alternating activity in reticulospinal systems.

Comparable tremor at rest follows injury to the dentate and interposed nuclei of the cerebellum (9), and it is stated that a background for its appearance is produced by lesions along a line traced from these nuclei through the brachium conjunctivum, the region of the rubrospinal tracts, Forel's fields, and the basal ganglia to the frontal cortex. Tremor, as the most conspicuous element of dysfunction, is encountered following lesions of Forel's fields, which appear to be the meeting point for those paths, cerebellar and other, which need to be damaged for the production of tremor (50). Lesions of the subthalamic nucleus are followed by more irregular involuntary movements of an athetoid or hemiballismal nature (51).

Spasticity.—The basic feature of the spastic state is a stretch

hyperreflexia, traditionally explained as a "release" from suppression exerted upon the cord by the pyramidal tract. Recent developments have shown, first, that the suppressor influence is mediated by an extrapyramidal system (43) and, second, that the stretch hyperreflexia consequent to its elimination actually depends upon the maintained and unopposed activity of central neural systems facilitating myotatic reflexes (2, 38, 43, 81). These latter findings document, some fifty years late, an alternative Jacksonian explanation of spasticity on an "influx" basis.

Somatic Sensation

Joint sensibility.—Articular nerve branches to the knee joint have been found afferent in nature, the fibers belonging to the A type, one group conducting at 70 to 90 meters per second and another at 20 to 40 meters per second (22). Their receptor endings are excited by pressure on the joint capsule and are slowly adapting.

Headache.—A classic series of clinical investigations upon headache have been collected into book form (84). Within the cranium, the large vascular channels and parts of the dura at the base are the only pain sensitive structures. The fifth nerve innervates those above the tentorium and the ninth, tenth, and upper three cervical nerves innervate those below it, with pain occurring respectively in front of or behind a line drawn from the ears to the top of the head. Headache may result from traction, displacement, distention, or inflammation of the innervated structures or from direct pressure upon the mentioned nerves. Headaches that arise primarily from intracranial sources result from tumors, meningitis, from distention of arteries by a variety of agents, or from spinal fluid drainage and introduction of air into the subarachnoid spaces.

The majority of headaches arising outside the skull result from distention of cranial arteries and from sustained contraction of muscles of the head and neck. Thus, migraine headache usually arises in distended branches of the external carotid artery and essentially the same mechanism is involved in producing the headache associated with arterial hypertension. Reflex contraction of the skeletal muscles of the head and neck, induced by any head pain, when prolonged, itself becomes painful. A small proportion of headaches results from inflammation and distortion of pain-

sensitive structures in the eye, ear, nasal and paranasal cavities, and teeth.

Hyperpathia.—The extremely unpleasant nature of pain in the thalamic syndrome, during the course of recovery from peripheral nerve lesions and in certain cutaneous scars, may also be induced by prolonged compression of an extremity (58, 67, 83), when pain from needleprick

> is felt, not as a bright flash, but as a slow, swelling, burning sting, which gives rise to a withdrawal reflex that is difficult to control and to other objective phenomena such as the appearance of sweat on the upper lip and contralateral palm, dilatation of the pupil and facial contortion. The subjective response may last for as long as ten seconds (83).

In all these conditions, the pain is paradoxic in being associated with cutaneous hypoalgesia, and histological study of hyperpathic scars revealed pain nets and terminals to be isolated from their neighbors instead of interweaving with them as in normal skin. It is proposed (83) that "the occurrence of over-reaction to painful stimuli in various clinical conditions is caused by a reduction in the normal pattern of impulses presented to consciousness."

Further references to current aspects of neurophysiology are to be found in seven other chapters in the present volume, and in the third volume of *Progress in Neurology and Psychiatry* (Grune and Stratton, New York, N. Y. 1948), which reviews over twenty-eight hundred articles.

LITERATURE CITED

1. ADRIAN, E. D., *The Physical Background of Perception*, 95 pp. (Clarendon Press, Oxford, 1947)
2. BACH, L. M. N., AND MAGOUN, H. W., *J. Neurophysiol.*, **10**, 331–37 (1947)
3. BAILEY, P., AND VON BONIN, G., *Trans. Am. Neurol. Assoc.*, 89–93 (1946)
4. BAILEY, P., VON BONIN, G., AND MCCULLOCH, W. S., *Anat. Record*, **100**, 5–6 (1948)
5. BARD, P., AND MOUNTCASTLE, V. B., *Science*, **107**, 457 (1948)
6. BARKER, S. H., AND GELLHORN, E., *J. Neurophysiol.*, **10**, 133–38 (1947)
7. BOSMA, J. F., AND GELLHORN, E., *Brain*, **70**, 127–44 (1947)
8. BREMER, F., *Arch. néerland. physiol.*, **28**, 481–87 (1947)
9. CARREA, R. M. E., AND METTLER, F. A., *J. Comp. Neurol.*, **87**, 169–288 (1947)
10. CARREA, R. M. E., REISSIG, M., AND METTLER, F. A., *J. Comp. Neurol.*, **87**, 321–66 (1947)
11. CHAMBERS, W. W., *Anat. Record*, **100**, 17 (1948)
12. CHANG, H. T., RUCH, T. C., AND WARD, A. A., JR., *J. Neurophysiol.*, **10**, 39–56 (1947)
13. CROSBY, E. C., AND HENDERSON, J. W., *J. Comp. Neurol.*, **88**, 53–92 (1948)
14. DAVISON, C., *Trans. Am. Neurol. Assoc.*, 112–17 (1947)
15. DELGADO, J. M. R., AND LIVINGSTON, R. B., *J. Neurophysiol.*, **11**, 39–55 (1948)
16. FIELDS, W. S., KING, R. B., AND O'LEARY, J. L., *Anat. Record*, **100**, 26–27 (1948)
17. FREEMAN, W., AND WATTS, J. W., *Proc. Roy. Soc. Med.*, **39**, 445–47 (1946)
18. FREEMAN, W., AND WATTS, J. W., *Arch. Neurol. Psychiat.*, **58**, 391–416 (1947)
19. FREEMAN, W., AND WATTS, J. W., *J. Comp. Neurol.*, **86**, 65–94 (1947)
20. FULTON, J. F., *Acta Med. Scand.*, Suppl. 196, 617–25 (1947)
21. FULTON, J. F., LIVINGSTON, R. B., AND DAVIS, G. D., *Federation Proc.*, **6**, 108 (1947)
22. GARDNER, E., *Am. J. Physiol.*, **152**, 436–45 (1948)
23. GELLHORN, E., *J. Neurophysiol.*, **10**, 125–32 (1947)
24. GIBBS, F. A., GIBBS, E. L., AND FUSTER, B., *Trans. Am. Neurol. Assoc.*, 180–82 (1947)
25. HALSTEAD, W. C., CARMICHAEL, H. T., AND BUCY, P. C., *Am. J. Psychiat.*, **103**, 217–28 (1946)
26. HAMPSON, J. L., HARRISON, C. R., AND WOOLSEY, C. N., *Federation Proc.*, **4**, 31 (1945)
27. HAMPSON, J. L., *Federation Proc.*, **7**, 50 (1948)
28. HERRICK, C. J., *J. Nervous Mental Disease*, **106**, 355–58 (1947)
29. HINES, M., *Federation Proc.*, **6**, 441–47 (1947)
30. INGRAM, W. R., WHEATLEY, M. D., AND KNOTT, J. R., *Anat. Record*, **100**, 46 (1948)
31. JASPER, H. H., AND DROOGLEEVER-FORTUYN, J., *Research Pubs. Assoc. Research Nervous Mental Disease*, **26**, 272–98 (1947)
32. JASPER, H. H., AND DROOGLEEVER-FORTUYN, J., *Federation Proc.*, **7**, 61–62 (1948)
33. KING, R. B., *Anat. Record*, **100**, 50–51 (1948)
34. KREMER, W. F., *J. Neurophysiol.*, **10**, 371–79 (1947)

35. KRIEG, W. J. S., *J. Comp. Neurol.*, **86**, 267–394 (1947)
36. KRIEG, W. J. S., *J. Comp. Neurol.*, **88**, 1–52 (1948)
37. LARRABEE, M. G., AND BRONK, D. W., *J. Neurophysiol.*, **10**, 139–54 (1947)
38. LINDSLEY, D. B., SCHREINER, L. H., AND MAGOUN, H. W., *J. Neurophysiol.*, (In press)
39. LIVINGSTON, R. B., AND FULTON, J. F., *Federation Proc.*, **7**, 74 (1948)
40. LLOYD, D. P. C., *J. Neurophysiol.*, **9**, 421–38 (1946)
41. LLOYD, D. P. C., *J. Neurophysiol.*, **9**, 439–44 (1946)
42. MAGOUN, H. W., *Anat. Record*, **100**, 120 (1948)
43. MAGOUN, H. W., AND RHINES, R., *Spasticity: The Stretch Reflex and Extrapyramidal Systems*, 59 pp. (Charles C Thomas, Springfield, Ill., 1948)
44. MARTIN, J., AND DAVIS, L., *Surg. Gynecol. Obstet.*, **86**, 535–42 (1948)
45. MCCULLOCH, W. S., *Federation Proc.*, **6**, 448–52 (1947)
46. MCCULLOCH, W. S., AND HENNEMAN, E., *Federation Proc.*, **7**, 79 (1948)
47. MCCULLOCH, W. S., AND LETTVIN, J. Y., *Ann. Rev. Physiol.*, **10**, 117–32 (1948)
48. METTLER, F. A., *J. Comp. Neurol.*, **86**, 95–117 (1947)
49. METTLER, F. A., *J. Comp. Neurol.*, **86**, 119–66 (1947)
50. METTLER, F. A., AND WHITTIER, J. R., *Trans. Am. Neurol. Assoc.*, 96–100 (1947)
51. METTLER, F. A., AND WHITTIER, J. R., *Trans. Am. Neurol. Assoc.*, 190–92 (1947)
52. METTLER, F. A., DAVIDOFF, L. M., AND GRIMES, R., *Arch. Neurol. Psychiat.*, **57**, 423–29 (1947)
53. MEYER, A., BECK, E., AND MCLARDY, T., *Brain*, **70**, 18–49 (1947)
54. NIMS, L. F., AND NULSEN, F. E., *Federation Proc.*, **6**, 170 (1947)
55. NULSEN, F. E., BLACK, S. P. W., AND DRAKE, C. G., *Federation Proc.*, **7**, 86–87 (1948)
56. OBRADOR, S., *J. Neuropathol. Exptl. Neurol.*, **6**, 185–93 (1947)
57. PAPEZ, J. W., AND VONDERAHE, A. R., *J. Neuropathol. Exptl. Neurol.*, **6**, 244–52 (1947)
58. PATTLE, R. E., AND WEDDELL, G., *J. Neurophysiol.*, **11**, 93–98 (1948)
59. PENFIELD, W., *Proc. Roy. Soc. (London)* [B]**134**, 303–28 (1947)
60. PENFIELD, W., *Psychical Seizures, in Psychiatric Research*, 83–99 (Harvard University Press, Cambridge, Mass., 1947)
61. PENFIELD, W., AND JASPER, H. H., *Research Pubs. Assoc. Research Nervous Mental Disease*, **26**, 252–71 (1947)
62. PEYTON, W. T., NORAN, H. H., AND MILLER, E. W., *Am. J. Psychiat.*, **104**, 513–23 (1948)
63. RANSTROM, S., *Acta. Path. Microbiol. Scand.*, Suppl. 70, 90 (1947)
64. RASMUSSEN, T., AND PENFIELD, W., *Federation Proc.*, **6**, 452–60 (1947)
65. REITMAN, F., *Am. J. Psychiat.*, **103**, 238–41 (1946)
66. RUCH, T. C., CHANG, H. T., AND WARD, A. A., JR., *Research Pubs. Assoc. Research Nervous Mental Disease*, **26**, 61–83 (1947)
67. SINCLAIR, D. C., *J. Neurophysiol.*, **11**, 75–92 (1948)
68. SMITH, W. K., *Anat. Record*, **100**, 81 (1948)
69. SNIDER, R. S., COOKE, P. M., AND HENNEMAN, E., *Anat. Record*, **100**, 125 (1948)

70. SNIDER, R. S., AND ELDRED, E., *Anat. Record*, **100**, 82 (1948)
71. SNIDER, R. S., MAGOUN, H. W., AND MCCULLOCH, W. S., *Federation Proc.*, **6**, 207 (1947)
72. SNIDER, R. S., AND MAGOUN, H. W., *Federation Proc.*, **7**, 117–18 (1948)
73. SORIANO, V., AND FULTON, J. F., *Federation Proc.*, **6**, 207 (1947)
74. SPIEGEL, E. A., AND WYCIS, H. T., *Federation Proc.*, **7**, 119 (1948)
75. SPIEGEL, E. A., WYCIS, H. I., MARKS, M., AND LEE, A. J., *Science*, **106**, 349–50 (1947)
76. SUGAR, O., CHUSID, J. G., AND FRENCH, J. D., *J. Neuropathol. Exptl. Neurol.*, **7**, 182–89 (1948)
77. VON BONIN, G., AND BAILEY, P., *The Neocortex of Macaca Mulatta*, 163 pp. (University Illinois Press, Urbana, Ill., 1947)
78. WALSHE, F. M. R., *Brain*, **70**, 93–104 (1947)
79. WALSHE, F. M. R., *Brain*, **70**, 329–54 (1947)
80. WARD, A. A., JR., *J. Neurophysiol.*, **11**, 13–23 (1948)
81. WARD, A. A., JR., *J. Neurophysiol.*, **10**, 89–104 (1947)
82. WARD, A. A., JR., MCCULLOCH, W. S., AND MAGOUN, H. W., *J. Neurophysiol.*, **11**, 317–30 (1948)
83. WEDDELL, G., SINCLAIR, D. C., AND FEINDEL, W. H., *J. Neurophysiol.*, **11**, 99–109 (1948)
84. WOLFF, H. G., *Headache and Other Head Pain*, 642 pp. (Oxford Univ. Press, New York, N. Y., 1948)
85. WOOLSEY, C. N., *Federation Proc.*, **6**, 437–41 (1947)

BIOELECTRIC POTENTIALS IN THE NERVOUS SYSTEM AND MUSCLE[1]

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A survey of the pertinent literature published during the period to which this review is primarily devoted reveals that a great deal of importance and interest has appeared, at the time of writing, only in the form of abstracts of papers presented at meetings of physiologists, in the form of lectures lacking printed documentation, or, for some other reason obviously is very incomplete. Clearly evident in these preliminary notes are indications of fundamental disagreement concerning the nature, or origin, and significance of certain electrical events within the nervous system. Such material, indicative of the current state of the subject, hardly lends itself to critical evaluation.

Interestingly the antithesis of the foregoing remarks is equally true. The review period includes the publication of, *A Study of Nerve Physiology*, by Lorente de Nó (1). This monograph brings to the study of bioelectric potentials concepts of such far-reaching consequence based on nearly a decade of active experimental analysis that critical review within any reasonable limitation of space is quite impossible. Selected portions can be touched upon in the present survey, but there is no short cut for the neurophysiologist. In the reviewers' opinion the brief treatment accorded the subject by Lorente de Nó in a Harvey Lecture (2) is a useful introduction to the monograph itself, but cannot in any way be regarded as an alternative source of information.

Concerning Nerve

Membrane potential and electromotive force (*E. M. F.*).—Recent reviews (3, 4) take note of the considerable dissatisfaction among investigating physiologists concerning hypothetical mechanisms underlying the existence of a membrane potential. The membrane theory itself, by which is implied here the "pre-existence" theory of Bernstein, is widely accepted. Ancillary to the membrane theory

[1] This review covers the period to July, 1948.

is the diffusion hypothesis advanced by Bernstein to explain the existence of a membrane potential. Both Grundfest (3) and Eccles (4) have discussed the more recent attempts to reach some formulation other than the classical diffusion hypothesis. These as well as the diffusion hypothesis itself now must be considered in the light of Lorente de Nó's exhaustive experimental treatment (1), in which he is led to discard the diffusion hypothesis because, at so many points, experimental result is not in accordance with prediction. For instance, while it is true that an increase in the external concentration of potassium decreases the membrane potential, the depolarization does not occur immediately, or as rapidly as may be, taking into account penetration of potassium ions into the nerve, nor, during the many hours required for the potassium effect to reach maximum, is the degree of depolarization produced by the potassium ions at any time in logarithmic relation to the external concentration of potassium.

Furthermore, if a segment of nerve, treated with 0.11 *M* KCL until depolarization is well advanced, is placed in potassium-free solution the membrane potential remains at a low value for an hour, thereafter slowly rising over an interval of many hours. Since an increase in external potassium concentration increases the internal concentration (5), shortly after placing the treated segment in potassium-free medium, the membrane potential should have been in excess of normal, decreasing thereafter towards normal with loss of the excess internal potassium ions.

It has long been known that membrane potential is dependent upon oxygen supply. In the light of the diffusion hypothesis it has usually been supposed that oxidative metabolism regulates the semipermeability of the membrane so that the potential can be maintained by outward diffusion of potassium. Such an indirect role of oxidative metabolism is called into question by experiments in which the effects of altered external potassium concentration and oxygen lack are superimposed (1). It has been found that absence of potassium ions from the external medium does not lead to essential change in the course of anoxic depolarization and oxidative recovery. In the potassium-free medium the nerves lose potassium during the anoxic period, and they cannot regain it during oxidative recovery. Thus, the absolute internal concentration and the ratio between internal and external concentrations of potassium are different in nerves maintained in Ringer's solution

and in potassium-free Ringer's solution. Since the course of oxidative recovery is comparable in the two situations it is concluded that those factors are not primary determinants of the resting membrane potential.

If segments of paired nerves are subjected to excess potassium ions, the one in oxygen, the other in nitrogen, it is found (1) that the nerve in nitrogen depolarizes at a higher rate. If, after depolarization has progressed for several hours, oxygen is readmitted to the anoxic nerve segment, it is repolarized in the course of minutes to a value of membrane potential higher than that of the treated segment of the companion nerve in oxygen and, in certain circumstances that are defined, to a value of membrane potential even exceeding that of an untreated segment. The rapidity of the postanoxic membrane repolarization makes significant change of internal potassium concentration an unlikely concomitant.

Briefly mentioned, the foregoing experiments are illustrative of the chain of evidence constructed by Lorente de Nó in presenting the view that oxidative metabolism directly establishes and maintains the membrane potential. The role of potassium is clear only to the extent that it must be subordinate to that of oxidative metabolism.

As was pointed out earlier there have been other attempts to replace the diffusion hypothesis. A major feature of these has been consideration of Donnan equilibria as mechanisms establishing the resting membrane potential. There would seem to be little doubt that a Donnan potential exists at the "membrane," but its value must be small, sufficient presumably to account for the anoxic residuum of membrane potential, but not more. In addition, hypotheses based upon Donnan equilibria cannot account for observations with nerve in potassium-free media.

In the concept of Lorente de Nó the membrane potential is regarded as an electrostatic potential that exists by virtue of a double layer at the boundary between internal and external conductors. Such a double layer is subject to electrostatic forces of attraction and would collapse if only electrostatic forces existed in the system. The double layer is maintained by short range chemical forces that tend to separate charged particles of opposite sign. These forces constitute the electromotive force (E. M. F.) of the membrane. The resting membrane potential difference is determined by the equilibrium between electrostatic (or Coulomb)

forces of attraction and chemical (or non-Coulomb) forces that act on the charged particles. If the electrostatic potential collapses at a point, as by injury, the non-Coulomb forces, by continually separating additional charges, maintain the flow of demarcation current. The nerve fiber "in so far as the resting membrane potential is concerned—is a self-contained system except in one aspect, namely that oxygen must be available to it" (1).

The primary importance now placed upon oxidative metabolism is reason enough to hope that careful and exhaustive studies may be forthcoming on the relation between oxygen consumption and membrane potential. It is gratifying that the perfection of technique for measurement of oxygen consumption is in progress at this time (6, 7), for it leads one to anticipate as well as hope that important advances will be made.

In a preliminary note Tobias (8) reports that muscles soaked in distilled water until potassium-free exhibit following a crush injury potentials of 9 to 30 mv. that fall to zero when the uncrushed surface is treated with 0.1 *M* potassium. Membrane potential measured by the use of an impaling microelectrode may be reversed from the usual orientation to as high as 40 mv. in comparable circumstances. Ling (9) adds that the membrane potential of normal single muscle fibers so measured is not affected by stretch.

Electrotonic potentials.—In an extensive analysis of electrotonus [(1), Chaps. 6, 7, 8 in particular] Lorente de Nó finds (*a*) that the electrotonic potential includes a number of components, E_1, E_2, and E_3; (*b*) that each component has characteristic features, E_1 for instance developing rapidly, E_3 very slowly; and (*c*) that each component to some extent may vary independently of the others. The three electrotonic potentials representing changes in the value of the membrane potential are related to three components of the latter: Q (for quick), M, and L (for labile). For many purposes it is permissible to consider only the Q and L fractions of membrane potential, and to speak of fast and slow electrotonus.

The spatial constants of fast and slow electrotonus are quite different, the former decrementing sharply, the latter spreading so that, at 15 mm. from the polarizing electrode the electrotonus is dominated by the latter. E_1, E_2, and E_3 deflections appear both at cathode and anode, and in each instance exhibit maxima during the flow of current that result from the reaction of the nerve to the

applied current. The E_1 reaction at the cathode has long been known as accommodation. After the end of current flow the operation of the nerve reaction causes the appearance of overshootings in each component of the membrane potential. It is obvious that the existence of overshootings of membrane potential in nerve must be of tremendous theoretical interest to those interested in electrochemistry.

As indicated by its designation, the L fraction of the membrane potential is very sensitive to external influences. Particularly striking is its relation to the carbon dioxide content of the surrounding medium. A nerve maintained in oxygen exhibits a very low value for the L fraction. Admission of 5 per cent carbon dioxide rapidly raises the L fraction to a high value. Cathode polarization reduces, anodal current increases the L fraction.

It is in the variability of L fraction that is found the explanation for many of the asymmetries between cathodal and anodal polarization. When the L fraction is small, it can be seen that the fast electrotonus is symmetrical at cathode and anode and stands in approximately linear relationship to the applied current. If the L fraction is large there is reasonable symmetry and linearity when small currents are applied, but with larger currents, slow anelectrotonus is greater than catelectrotonus. Also if the L fraction is reduced as by cooling, or in the early stages of etherization, anelectrotonus is the greater. A simple explanation is that cathodal polarization can only remove what L fraction there is, whereas anodal polarization builds up the L fraction. It is noted that characteristic curves relating amplitude of electrotonus to magnitude of applied current are not sufficient to characterize the responses, for differences may occur in the rate at which electrotonic potentials are established at anode and cathode.

Hodgkin (10) presents data on membrane resistance and capacity, and on the specific resistance of the axoplasm of Carcinus axons as information preliminary to the use of these axons in preference to those of the squid or lobster. Then employing an ingenious electrode arrangement by which the voltage drop along the longitudinal resistance of the interpolar region is balanced out, and the membrane current flows in a region that can be subjected to fluids of altered composition, Hodgkin (11) has investigated the action of potassium and related ions on the change in membrane potential produced by a given anodic flow of applied current. By the use of

the interpolar recording arrangement, and by extrapolar recording, it is found that the change in membrane potential caused by the standard applied current is increased by potassium-free Ringer's solution and decreased by increased potassium concentration in the external medium of the test segment. Sodium had but a slight effect, and the effect of acetylcholine was negligible.

Hodgkin & Huxley (12) describe the cumulative effect of trains of impulses upon the extrapolar anelectrotonus in single Carcinus axons. Following activity the anelectrotonic potential produced by a given applied current is reduced, the effect dying away in the course of minutes. Washing the axon in sea water greatly accelerates the disappearance of the effect. Prolongation of the stimulation and increase in frequency of stimulation both augment, increasing the volume of external medium diminished the effect.

Building upon the evidence derived from extensive work on invertebrate axons, Hodgkin & Huxley employ the changes in amplitude of electrotonus produced by a standard applied current as indicative of changes in membrane conductance, a decrease in the membrane potential response, as with increased potassium concentration, or following rhythmic activity, naturally indicating increased membrane conductance. The fact that washing an axon in sea water hastens recovery from the effects of rhythmic activity is good evidence that something leaks out of the fiber during the activity to produce the effect, and Hodgkin & Huxley present a reasonable case for the something being potassium. However, it is only fair to remark that if invertebrate axons prove eventually to have properties resembling those of frog fibers rather more than those of passive models, the validity of some fundamental assumptions underlying the interpretation of electrotonic changes in invertebrate axons may require re-examination. As far as the reviewers' insight has permitted comparison to be made, the experimental findings of Hodgkin and of Hodgkin & Huxley are in considerable degree not incompatible with other interpretations.

Oscillation and repetitive actions have received much attention in recent years. To the publications reviewed in recent volumes there may be added the recent paper of Hodgkin (13) dealing with the phenomenon as seen in isolated axons of Carcinus and the many observations published by Lorente de Nó (1).

Strohl & Desgrez (14) raise a number of questions concerning spike conduction through a polarized zone and find that the effect

produced by a current flow depends upon the length of time it flows before impulse conduction is tested. The desirability of great caution in chronaximetric analysis and interpretation is stressed (15). Göthlin & Löfgren (16) present a broad discussion of the factors that constitute electric excitation in peripheral motor axons. Physical chemists in particular will be interested in their consideration of electrostenolysis.

Von Euler (17) notes an interesting difference between autonomic and somatic C fibers with respect to their responses to a constant current. Vagus nerve fibers do not fire repetitively to currents of four × rheobasic strength, whereas dorsal root vasodilator fibers, stimulated by currents just over rheobasic strength, yield evidence of so doing. Differences in accommodation are suggested in explanation.

Actions of ions.—Maintenance of the membrane potential is not a sufficient condition for initiation and conduction of a nerve impulse (1). A nerve kept in choline chloride for more than about six hours becomes inexcitable. The addition of potassium ions or calcium ions will not prevent the loss of excitability, nor restore it once lost, but sodium ions do. Failure of excitability in sodium-free medium is not the result of depolarization, for indeed the membrane potential may be increased slightly. Hence, sodium plays a specific role in the mechanisms underlying the production of a nerve impulse. Nerves in sodium-free media may be polarized, but the E_1 fluctuation disappears as the nerve becomes inexcitable and the nerve reaction including the overshooting following the end of current flow is lost. This is to say that the nerve loses the power to regulate the E. M. F. of its membrane in response to applied currents.

During the passage of an impulse the membrane potential collapses. The Q fraction of the membrane potential is restored during the descending limb of the spike, the L fraction during the negative after-potential. Positive potentials that follow the passage of nerve impulses are comparable to the overshootings following the end of applied cathodal currents. Specifically it is the E_1 reaction that restores the Q fraction of the membrane potential following the passage of a nerve impulse. It comes as no surprise, then, that sodium ions play a specific role in recovery after the passage of nerve impulses.

Graham & Blair (18) present detailed observations upon the

effects of associated changes in concentration of potassium and calcium ions, showing that increased potassium decreases the amplitude of spike and negative after-potential, slows conduction velocity and recovery after conduction. Calcium ions in general exert opposite effects.

Lorente de Nó (1) reports that increase in the concentration of calcium ions in the external medium of respiring nerve first increases the membrane potential, then causes progressive depolarization. Such depolarization is largely irreversible and affects predominantly the large myelinated fibers. Analysis of these effects leads to the conclusion that excess of calcium ions increases the L fraction of the membrane potential initially without affecting the Q fraction. As depolarization sets in, the Q fraction becomes reduced, while the L fraction remains high. Anodal currents reinforce the calcium block ; cathodal currents tend to relieve it, but because of the low Q fraction, the nerve rapidly passes into the depressed state and conduction fails again.

Lowering the concentration of calcium ions is generally believed to favor the initiation of rhythmic activity in nerve, and further results consistent with this view have been reported (19, 20). Lorente de Nó, however, advances strong arguments in favor of the view that the spontaneous firing observed in experiments of this kind is brought about by a direct action of "decalcifying" agents such as oxalate and citrate, and not primarily as a result of the removal of calcium ions (1). The action of barium upon nerve has also been investigated recently (21). According to the results of this study, barium ions exert a depolarizing action over a wide range of concentrations, in many respects like that of calcium ions. Lowering of membrane potential is preceded by a phase of hyperpolarization in the presence of oxygen and carbon dioxide. Barium appears to increase the L fraction of the membrane potential while at the same time the total membrane potential diminishes through loss of Q fraction, so that the changes in stimulation threshold are complex. Conduction block is eventually produced, at first reversible and relieved by anodal current, later irreversible. As in the case of calcium, myelinated fibers are more susceptible to the action of barium ions than unmyelinated. However, barium-treated nerve is readily set into rhythmic activity and shows spontaneous, slow oscillations of potential. Excess of magnesium ions exerts an effect somewhat like that of increased calcium ion

concentration, depolarization following an initial slight increase in the membrane potential of respiring nerve. However, the depolarization is not so rapid or severe as it is with excess of calcium ions and does not seriously impair the mechanisms underlying excitability, so that complete recovery readily takes place (1). Cupric ions depolarize nerve membrane irreversibly, but for a considerable period excitability can be restored by applying anodal current. Eventually, cupric ions appear to poison essential enzymatic systems irreversibly.

Other ions, the effects of which upon nerve have been investigated, include rubidium, ammonium, cesium, and lithium. Hodgkin (11) grades the effectiveness of monovalent cations in reproducing the potassium effect on electrotonus in Carcinus axons as follows: rubidium, potassium, cesium, sodium, and lithium approximately forty times the molar concentration of the last two being required to mimic the action of the first two named. Gallego & Lorente de Nó (22) report the depolarizing action of rubidium ions to be virtually identical with that of potassium ions. Ammonium, cesium, and lithium ions also produce depolarization of the nerve membrane, but there are significant differences in the manner of onset and of recovery after transfer to Ringer's or an indifferent solution. Unless the nerve remains in the test solutions after depolarization becomes total, the effects are fully reversible, except in the case of lithium ions which produce irreversible changes in the nerve even before the membrane potential is greatly reduced.

It must be emphasized that in virtually all these studies with inorganic ions, no direct information is available correlating various functional states with the actual amounts of the test ions present within the nerve fibers. Accurate, direct estimations of intra-axonal concentration of various substances and of their rate of uptake or outward diffusion under different conditions will provide information of great importance in assessing the significance of each ion in the metabolic cycle of nerve. A method that may yield useful information is the use of radioactive isotopes (23).

Action of anesthetic agents.—Analysis of the effects upon nerve function of alcohol, ether, ethyl urethane, and cocaine (1, 24) demonstrates strikingly the inadequacy of studies based solely upon the criterion of the ability of a nerve to conduct impulses. All four of these substances can render a nerve inexcitable; but the mecha-

nism of block by the first two mentioned agents is quite different from that brought about by the last two. Alcohol and ether are depolarizing agents and block conduction through lowering the membrane potential below the critical level; but they have no action upon the excitable mechanism proper, for excitability of the treated nerve may be restored by anodal polarization. Cocaine and ethyl urethane, on the other hand, have very little direct action upon the membrane potential and prevent the propagation of impulses by a specific action upon the excitable mechanism. Cocaine and ethyl urethane block cannot be relieved by anodal polarization. Cocaine is reported to have actions consistent with the view that it reduces membrane permeability to potassium (25). Accompanying the observations is an hypothesis postulating that the rate of outward transport of potassium at the stimulating cathode is the controlling factor in excitation and that cocaine acts by reducing this rate of transport. The consequences of this hypothesis are interesting but largely untested. An extensive comparison of magnesium anesthesia and ether anesthesia has been made by Engbaek (26).

Metabolic inhibitors.—Study of the effects of various metabolic poisons had been undertaken with the object of providing clues as to the nature of the metabolic processes in nerve responsible for maintenance of the membrane potential and the mechanisms underlying the phenomenon of excitability (1). Cyanide, as expected, depolarizes nerve in much the same manner as lack of oxygen. Conduction block is mainly referable to this loss of membrane potential and can be relieved by anodal current, at least with concentrations of sodium cyanide not greater than 0.05 *M*.

Phloridzin has no depolarizing action upon nerve, in fact it tends to increase the L fraction of the membrane potential. However, eventually this substance brings about blockage of conduction, not relieved but, if anything, reinforced by anodal currents. It appears to have a direct action upon the excitable mechanism and can be classed as a narcotic along with cocaine. Iodoacetamide causes after an initial increase in membrane potential, an incomplete depolarization of respiring nerve, much like the effect of anoxia; conduction block is indirect and can be relieved by the passage of anodal current. The action of veratrine, long known to have a profound effect upon nerve and muscle, has also been analyzed. The strong depolarizing action of this substance is like that

of potassium but is more completely counteracted by the presence of 5 per cent carbon dioxide. Interference with conduction of impulses is referable to the loss of membrane potential and not to any direct effect of veratrine on the excitable mechanism. The series of papers dealing with the influence of esterase inhibitors will be considered in a separate section.

Other organic substances.—Triturus toxin, an agent of unknown nature, blocks frog A fibers reversibly, and with dramatic suddenness (27). Recovery after washing likewise is rapid. In the absence of fuller analysis, the mechanism by which the agent blocks conduction remains obscure.

Thiamine chloride in isotonic solution, after an initial latent period, depolarizes nerve fibers and renders them irreversibly inexcitable in about three hours, regardless of the presence or absence of oxygen (1). At no stage can conduction be improved by the passage of anodal current, indicating that the damaging action of thiamine is exerted directly on the excitable mechanism.

Although isotonic sucrose and galactose solutions bring about an increase in the resting membrane potential of nerve, the effect is referable rather to lack of sodium ions than to a direct influence of these sugars. On the other hand, isotonic solutions of glucose and levulose have a profound effect in the absence of oxygen, although without appreciable direct action upon respiring nerve. Anoxic depolarization is delayed, but after a relatively short time the presence of these sugars effects irreversible damage to the nerve fibers. This appears to be the result of a direct action upon the excitable mechanism, as the membrane is only slightly depolarized at the time of failure, and conduction cannot be restored by the action of an anodal current.

Further studies have been made of the effects of organic anions such as lactate, acetate, oxalate, and citrate. The last two have long been known to initiate spontaneous firing of impulses. Monnier (19) reports experiments in which calcium-free Ringer's solution containing sodium oxalate or citrate, in association with temperature fluctuations, provoked strong, often highly synchronized, spontaneous rhythmic firing of frog sciatic nerves, this being interpreted as a manifestation of the removal of ionic calcium. Solutions containing phosphates of sodium were also reported to have a similar action and were used in experiments designed to demonstrate a similar augmentation of reflex auto-

rhythmicity in spinal frogs (20). On the other hand, evidence has been presented indicating that the spontaneous firing of nerve in the presence of oxalate or citrate is primarily a direct action of these organic anions (1). Similar spontaneous firing is observed with lactate and acetate, although the latter ion has, in addition, a specific injurious effect upon nerve leading to depolarization and irreversible loss of excitability. Oxalate and citrate exert a mild depolarizing action upon nerve, involving a relatively greater decrease in Q fraction than in L fraction, a condition favoring the occurrence of rhythmic firing, and counteracted by any agent which increases the L (and indirectly, the Q) fraction of the membrane potential, such as carbon dioxide, magnesium, or calcium ions (1, 21).

Acetylcholine and nerve.—During the past few years waning interest in acetylcholine has been revived by the appearance of di-isopropylfluorophosphate (D. F. P.), which substance has now been widely investigated with differing results upon excitable tissues and convictions. Actually, within the period covered by this review, very little material has appeared which sheds fresh light on the problem, and the reader is referred to the reviews of Grundfest (3), Nachmansohn & Rothenberg (28), Gerard & Libet (29), Nachmansohn (30), and Gerard (31) for the earlier background of the present controversy. It will be recalled that the close parallelism claimed by proponents of the hypothesis between cholinesterase activity in nerve and ability to conduct impulses has been challenged in some quarters (32, 33), conduction of impulses being demonstrated in nerves believed to contain no appreciable amounts of cholinesterase. Technical inadequacies in the latter studies, leading to misleadingly low figures for esterase content, are considered by Nachmansohn and his co-workers to account for these findings; repetition of the experiments under slightly different conditions indicated an actual esterase content of D. F. P. treated nerves which had retained or recovered their excitability amounting to 30 to 40 per cent of the normal value (34, 35). On the other hand, experiments by Chadwick & Hill (36) upon roaches led them to the conclusion that conduction can be unimpaired in the presence of concentrations of D. F. P. sufficient to abolish all cholinesterase activity. In a study undertaken by Toman *et al.* (37) with the object of testing whether conduction block by esterase inhibitors is actually brought about by accumu-

lation of acetylcholine (as the acetycholine hypothesis demands), no evidence of progressive depolarization before loss of excitability was afforded by determination of demarcation potential, stimulation threshold, and conduction velocity [compare, however, Lorente de Nó's experiments with 0.01 *M* eserine sulfate, which produced rapid depolarization of nerve fibers (38)]. Confirming Lorente de Nó further experiments (37, 39) failed to reveal any blocking action of acetylcholine when protected from hydrolysis, upon nerve even after prolonged exposure to isotonic solutions of this substance. Two alternative explanations were given (37): either acetylcholine fails to penetrate the nerve fibers, or more likely, that it plays no direct part in the conduction of impulses, nor in the action of D. F. P. and other anticholinesterases. Among the latter, there is stated to be a lack of parallelism between esterase inhibiting power and ability to modify nerve conduction (39) or central nervous system activity (40). The powerful effects upon frog brain preparations of metabolic inhibitors, other than anticholinesterases, have also been pointed out (40).

Attention having been directed to the existence in squid nerve sheath of another powerful enzyme adenosinetriphosphatase (41), one encounters the prompt rejoinder that, in frog nerve, the adenosinetriphosphatase activity is unchanged by concentrations of anticholinesterases that block conduction (42). Other reports have appeared dealing with acetylcholine and phase-boundary potentials (43), although the relationship of these observations to the problem of nerve conduction remains obscure. It is clear that much of this material has no crucial bearing on the central core of the acetylcholine hypothesis. As yet unanswered, however, by proponents of this hypothesis is the observation by Lorente de Nó (1) that nerve, depolarized and rendered inexcitable by large amounts of eserine, regains its ability to conduct impulses upon the passage of a weak anodal current, even in the continued presence of eserine. At least this particular esterase inhibitor, therefore, blocks conduction by virtue of its depolarizing action, and not through direct interference with any part of the excitable mechanism. Weaker concentrations of eserine or of D. F. P. are virtually without effect upon nerve function, as are massive concentrations of acetylcholine provided hydrolysis is prevented (1, 38); it has been suggested that the eventual depolarizing action of high concentrations of acetylcholine not protected from hydrolysis by

esterase inhibitors is the result of the specific action of acetate ions, since acetate is known to exert an injurious effect upon nerve, and since choline, the other product of hydrolysis, is so inactive as to form, in isotonic solution, the ideal indifferent medium for nerve studies (1). To explain the lack of action of acetylcholine upon nerve, Nachmansohn (44) has postulated that this substance, when applied in the course of an experiment, fails by virtue of its molecular configuration to penetrate the lipoid membrane of the nerve fibers, and therefore cannot be expected to reproduce the effects achieved by the acetylcholine liberated naturally; direct estimations, in squid giant axons, of axoplasmic acetylcholine tagged with radioactive nitrogen, have lent support to this suggestion (45, 46). On the other hand, Lorente de Nó (1) advances strong arguments to the effect that the nerve membrane is freely permeable to acetylcholine and other substances. Timely comments [(1) Part I, 240–43)] upon the inadmissible criteria usually adopted in deciding whether or not a given substance penetrates the nerve membrane deserve careful consideration, in view of the far reaching theoretical implications involved in this question.

Thermal influences on nerve.—Considerable attention has been devoted to the influence of temperature changes upon the resting membrane potential, spike and after-potentials, electrotonic potentials, and other phenomena of living nerve fibers. Lorente de Nó (1) presents many observations on the effects of cooling nerves. Changes in the membrane potential in the main are confined to the L fraction, which is markedly reduced as shown by the fact that increase in an applied current causes little increase in the slow catelectrotonus while producing a large increase in the slow anelectrotonus. Little change in Q fraction accompanies cooling of a nerve with the result that a nerve in the state of cold block may have a membrane potential comparable to that of a nerve at "normal" temperature in oxygen. It follows that a cold block is not due to depolarization beyond a critical level, but, on the other hand, it is relieved to some extent by anodal polarization, a property for the most part of blocks produced by depolarizing agents. Indeed, in all essential aspects changes in the action potential induced by lowered temperature resemble those induced by anoxia and depolarizing agents.

An important paper by Bremer & Titeca (47) relates to the influence of temperature change upon various properties of frog

nerve, particularly with regard to the establishment of reversible heat block. In agreement with Lorente de Nó's results, and those earlier observers, it is found that little change in resting potential occurs as the nerves are cooled below the optimum temperature, but with warming the resting potential decreases progressively to a low value. Amplitude of the spike potential varies rather evenly over a considerable temperature range on either side of the optimum, but, while cold block would appear to be established in a progressive manner, heat block has a sudden onset within a narrow critical temperature range (31° to 33°C.) If the critical temperature is not greatly exceeded nor maintained for too long a period the heat block is fully reversible. Through most of the temperature scale conduction velocity varies with temperature, but in the range just below establishment of heat block the trend reverses and conduction velocity decreases markedly with each increment in temperature. In the same range threshold of the nerve rises rapidly.

Prolonged subjugation of a nerve to blocking temperature or repeated application of blocking causes a progressive elevation of the critical blocking temperature, but a nerve maintained for relatively long periods at a temperature just below the critical blocking level shows no corresponding adaptation. Alpha, beta, and gamma fibers have different sensitivity, alpha fibers blocking at the lowest temperature, gamma fibers being the most resistant. Particularly interesting to many will be the demonstration that conduction fails before excitability as temperature rises.

Lundberg's monograph on temperature effects in nerve (48) has especial interest, being concerned with a comparison of mammalian A and C fibers. The two fiber types exhibit marked differences to warming and cooling. In motor root A fibers membrane potential and negative after-potential are maximal at 37°C., but the spike potential is maximal between 30° and 35°C. In sympathetic C fibers, by way of contrast, membrane and negative after-potentials are maximal at 25°C. while the spike is maximal at 5° to 10°C. These results are in interesting contrast with amphibian nerve, wherein the maxima tend to coincide with the temperature at which the animals have been acclimatized. Of fundamental importance is the observation with C fibers because the tremendous increase in spike potential brought on by lowering the temperature below 25°C. takes place in the face of a decreasing membrane potential to present further evidence against the simple view that

the spike is merely a disappearance of the resting membrane potential. The observed parallelism between change in membrane potential and negative after-potential, as Lundberg points out, suggests that change in the L fraction of Lorente de Nó is the major component in the temperature response. In this respect, therefore, the reaction of frog and mammalian fibers to temperature change seem comparable.

In studying the thermal response of nerve on a background of altered potassium concentration Lundberg has discovered that in general a reduction of potassium in Ä fibers makes them resemble normal C fibers in so far as thermal sensitivity is concerned, whereas increase in potassium makes the thermal properties of C fibers resemble those of normal A fibers.

Electrolyte concentration and nerve.—In an investigation of the effect of electrolyte concentration upon conduction velocity, Katz (49) reports that velocity in a single crustacean axon diminishes with decreasing salinity of the sucrose-sea water mixture bathing the preparation, more or less in accordance with predictions of the local circuit theory. Similar experiments upon frog sciatic nerves with isotonic sucrose (1) revealed very little change in the speed of conduction, apparently referable to the increase in L fraction of the membrane potential brought about by the test solution with resultant increase in spike height, which, by tending to increase conduction velocity, counteracted the effects of low conductivity in the external medium. In addition, an important return path for current flow is provided by the fibers themselves in such a multifibered preparation. In another study (50) of the effects upon frog nerve of solutions of low electrical conductivity, marked slowing of conduction rate was observed with glucose-bicarbonate solutions. It is, however, unlikely that such slowing can be attributed to low conductivity of the medium, as there also occurred signs indicating a profound alteration in the state of the nerve membrane.

Potentials in and about Junctional Regions

Unquestionably the most important single problem in this field of activity is that of determining the properties of the elements, presynaptic and postsynaptic, that enter into the formation of synapses. The term "synaptic potential" has been much used by neurophysiologists, and with such variable connotations that it

now may be said to have no specific meaning whatever. Apparently Fessard & Matthews (51) introduced the term to describe certain events that previously had been called dorsal root potentials (52). Eccles, on the other hand, uses the term to indicate a negative potential recorded from postsynaptic structures in the absence of discharge, as, for instance, in the blocked sympathetic ganglion (53) or spinal cord (54). In the latter case there is described a ventral root synaptic potential (54, 55), and a focal synaptic potential (55). The focal synaptic potential is recorded during the course of monosynaptic reflex excitation and in the absence of motoneuron discharge by means of a microelectrode placed in a motor nucleus. There is some room for doubt concerning the validity of the assumption that the focal and ventral root "synaptic potentials" may be identified one with the other. Bremer (56) chooses a broad view: that the importance of "the prolonged negative potentials of the spinal cord—which diffuse electrotonically along ventral and dorsal roots" justifies the epithet of "synaptic." Accordingly Bonnet & Bremer (57) speak of "potentials synaptiques dorsaux ou ventraux." But one may wonder if the slow positive potentials that Bernhard (58) and Bernhard & Skoglund (59) quite reasonably call ventral root potentials might not, to the same degree as their negative counterparts, merit inclusion in the category.

The most serious objections to a term such as "synaptic potential" would seem to be that its use invites confusion as to meaning and implies the existence of knowledge that in fact we do not possess, thereby obscuring the real problem of determining, wherever possible, the origin of a given potential difference. The efforts of the Stockholm group (58 to 66) to account for the origins of the negative and positive ventral root potentials they have recorded constitute a notable example of refusal arbitrarily to designate such origins and mode of production.

Concerning the fundamental properties of transmission in monosynaptic reflex systems little new has appeared in other than abstract form (67, 68). From preliminary indications it seems quite certain that discussion, and possibly controversy, will center about the respective roles of presynaptic and postsynaptic structures in the production of various synaptic phenomena. The present reviewers feel diffidence in discussing the problem as it now stands prior to full publication of experimental evidence and current concepts.

In an impressive series of progress reports from the Nobel Institute and Physiology Department in Stockholm (58 to 66, 69) the results of broad survey experiments in various parts of the nervous system are presented. These center about the main theme that direct currents of opposite direction produce opposite actions in the antagonistic mechanisms of the nervous system and that the antagonistic mechanisms, flexor and extensor, in action, produce potentials of opposite sign recordable, for instance, by ventral root leads. The present series of papers define the problem that is to be solved. In each situation under study it is felt by the group that the phenomena may be due to differences in anatomical orientation of elements with respect to current flow, or to fundamentally different inherent properties of the neurons pertaining to antagonist systems.

Operating within the general framework of thought von Euler & Skoglund (69) have employed nerve as a model, investigating the effect upon nerves of various fiber constitutions, of ascending and descending currents. It was their practice to place one stimulating electrode at the crushed end of the nerve, the other at a distance of 10 mm. The analysis concerns responses at the closing current. Briefly stated, under the experimental conditions, A or B fibers (depending on the choice of nerve) are more easily excited by descending current (physical anode at the crushed end), C fibers by ascending current, the differential being such that, by ascending current of carefully chosen strength, C fibers may be stimulated in isolation. Here then is an important achievement, clearly demonstrated, although, as the authors state, the differences are not easily explained on the basis of present knowledge. It would seem highly significant that the C fibers alone are more easily excited when the cathode is situated on the crushed region of a nerve. It is well known, and well illustrated in the paper under discussion, that the responses of C fibers are not easily rendered monophasic by crushing, a fact that may indicate that the C fibers exhibit in the region of a crush a physiological condition that differs widely from that of A or B fibers.

As reported in two papers (60, 61) Skoglund finds, on exposing the spinal cord or the medulla to current flows of different directions, that, for a given placement of electrodes current in one direction causes responses mainly in flexor muscles, and in the reverse direction causes responses mainly in extensor muscles. When back-

ground activity is present it is inhibited in reciprocal relation to the excitatory effects.

Bernhard & Therman (62, 63, 64) have continued their study of rhythmicity and rhythmical alternations of facilitation and inhibition in ascending long spinal reflexes, and in stretch reflexes, with a view to possible correlations between the direction of excitation and the sign of recorded potentials, and to possible substantiation of the hypothesis that flexor and extensor neurons possess fundamentally different properties. Bernhard & Therman lean toward the view that the rhythmicity is centrally determined since they could observe cyclic facilitation and inhibition of a myotatically maintained motoneuron discharge following nerve stimulation at a strength "too low to give contractions in the muscles in question." There may be some who will not regard as established the conclusion that the cyclic changes of excitation are not governed by proprioceptive inflow, for no account is taken of the virtual certainty that the initial change in level of motoneuron discharge must alter the mechanical state of the muscles and so must alter in turn the level of myotatic inflow to the spinal cord. One must remember that a 10μ stretch of a 40 mm. muscle is sufficient to elicit a jerk response (70).

Following an earlier lead (71) Bernhard (58), Bernhard & Skoglund (59), and Bernard, Skoglund & Therman (65) have recorded ventral root potentials in a variety of situations finding a variety of complex wave patterns, the simplest of which, however, are to be seen following medullary stimulation designed to evoke flexion or extension. Mindful of the fact that the discharge of motoneurons results in complication of the ventral root recordings, Bernhard & Skoglund lower the stimulus strength to a value subliminal for motoneuron discharge to record simple potential waves having, however, determined whether the stimulation in greater strength produces flexion or extension. In this fashion they find a negative wave caused by flexion-producing stimulation, a positive wave by extension-producing stimulation. The potentials presumably are associated in some way with rebound from the initial actions, for in the particular instances in which the Stockholm group present curves plotting reflex excitability the rule seems to hold that extensors are facilitated during root negativity whereas flexor reflex discharges are depressed.

Several papers (72, 73, 74) deal with spontaneous electrical

activity of the spinal cord and the effect upon it of various experimental procedures. Renshaw & Rosenbaum (75) ask whether injury to an axon promptly induces altered excitability in its cell of origin, and provide the brief answer that it does not. One may find several preliminary notes relating to the problem of central inhibition (67, 76, 77) that give promise of providing, when published *in extenso*, material for discussion in subsequent reviews.

Activity of neuron somata.—For many years a fascinating subject for speculation, the problem of conduction in the cell body and dendrites is at last beginning to yield information in the face of systematic investigation. Not the least important aspect of Lorente de Nó's analysis (78) of the action potential of motoneurons following antidromic stimulation is the re-emphasis of the fundamental necessity for a certain understanding, in every investigation of electrical activity of nervous tissue, of the anatomical details of the tissue studied and the conditions of recording. The need for such understanding is nothing new introduced into neurophysiology with the advent of the direct approach by means of microelectrode recording to the problems of action within the central nervous system. True, the anatomical situations are new and varied, and the conditions of recording different, but the understanding of them is no more and no less necessary for interpretation of potentials recorded in a nucleus than it has been for interpretation of a monophasic spike potential in peripheral nerve.

Lorente de Nó (78) has shown that progression of impulses along the intramedullary segment of motoneuronal axons is continuously progressive. Curiously enough the cell body of motoneurons repolarizes faster than do the initial segments of the axons with the result that the axons do not act as sources of current for the cell bodies and the spike potential recorded from them is diphasic. Thus, after the antidromic impulses enter the somata, the currents flowing between parts of the axons and those flowing between parts of the somata are largely independent systems.

The fields of somatic action currents depend largely upon the geometry of the active nucleus. From his study of nuclear structure Lorente de Nó recognizes three elementary configurations: (*a*) cell bodies located centrally with dendrites radiating to the periphery of the nucleus; (*b*) cell bodies at the periphery with dendrites radially orientated toward the center of the nucleus; and (*c*) a "polar" arrangement such, for instance, as that of the

Betz cells of the motor cortex. In the first two nuclear configurations the lines of current flow are orientated radially so that the equipotential lines are circular and the potential at the boundary of the nucleus is zero. It is only with the "polar" configuration that an open field is established and somatic current spreads to some distance outside the nucleus.

As a consequence of the radial arrangements (*a*) and (*b*) the somatic action potential is diphasic, negative-positive in (*a*), positive-negative in (*b*). Where an open field exists by virtue of "polar" configuration the somatic action potential is diphasic at the cell body and at the dendrite tips, but in between it is triphasic.

Impulses travel over the soma at an average velocity of about 2 meters per sec., or somewhat less than one-fiftieth the velocity of propagation in the axons. At the terminal regions of the dendrites the second (negative) phase of the action potential has a duration of no less than 5 to 8 msec., and as a matter of interest, bears a striking resemblance to the action potential of primary afferent endings (78).

An analysis of the conduction properties of the intramedullary portion of afferent neurons has appeared in preliminary form (68, 79), as has consideration of the cord potential following dorsal root stimulation (80).

Other elementary synaptic systems.—Bronk, Larrabee & Gaylor (81) employ the sympathetic ganglion as a convenient test system for comparing the effect on synaptic and axonal conduction of anoxia and circulatory arrest. Axonal and synaptic conduction fail with approximately the same rapidity indicating that, in sympathetic ganglia at any rate, cell bodies and synaptic mechanisms are not markedly more sensitive than axons. Failure of the synaptically relayed pathways is hastened by rhythmic activity. Sensitivity of the postganglionic neurons to acetylcholine fails in parallel with orthodox synaptic transmission, as does that to injected potassium chloride, indicating that failure of the postsynaptic neurons is a sufficient explanation of the anoxic failure. To parallel this interpretation Lloyd & McIntyre, utilizing asphyxia as an investigative tool in studies on the dorsal root potential (68), adduce evidence to the effect that postsynaptic failure antecedes, by a brief interval, failure at the region of branching of the presynaptic dorsal root fibers. Utilizing a different experimental approach and different concepts as to the nature of the fundamental processes

in synaptic transmission, Brooks & Eccles (82) suggest that the initial failure of orthodromic conduction occurs in the presynaptic fibers. Actually there are many strategic points wherein failure may occur [consider also the initial segment of the axon in the instance of experiments utilizing antidromic conduction (78) and presumably in orthodromic conduction as well], and the time differential is small for failure at one or another of these strategic points compared with that for failure of any of these and failure of the presynaptic and postsynaptic axons, that differing techniques alone could well lead to different conclusions.

Brief notes (83, 84) indicate that studies on narcotics as they effect axons and synapses may be forthcoming to complement those on circulatory arrest and anoxia, and that a comparative study will bring forth much of interest.

Feldberg & Hebb (85) find that adenosinetriphosphate and creatine phosphate stimulate the superior cervical ganglion even after degeneration of the preganglionic fibers. Adenylic acid and sodium tri-, pyro- and orthophosphate are fully as active, but creatine and adenosine have no effect, suggesting that phosphate per se is responsible for the action. Since the effects are not blocked by curare they are not similar to that of acetylcholine.

Eccles (86) shows that the actions of anticholinesterases and acetylcholine in the isolated frog cord preparation are inconsistent with any notion that acetylcholine mediates synaptic transmission in the spinal cord. He further points out that the frequently made comments about quaternary ammonium compounds and myelin cannot be raised in objection to his experiments. Of course, the same is true of the now long standing observations of Bronk (87) with sympathetic presynaptic fibers, and probably quite generally.

Van Harreveld & Feigen (88) note that small doses of nicotine depress the knee-jerk and monosynaptic reflex discharges, and to some extent the flexor reflex, whereas large doses increase the reflex discharges.

Invertebrates present interesting instances of simple synaptic systems that are beginning to attract investigation. A recent review by Bullock (89) may be used as a reference source to work in this field. At the present time the influence at these junctions of various substances is actively studied (90, 91, 92), but the fundamental properties of invertebrate synapses have been studied as yet less intensively than those of sympathetic ganglia and central

nervous system of vertebrates.[2] From published accounts it would seem that the properties of invertebrate and vertebrate nerve fibers alone are so different that precautions should be taken to avoid, at the present time, too close an analogy between the properties of synapses in the two groups.

Junctions of nerve with muscle.—Kuffler & Gerard (93) and Kuffler, Laporte & Ransmeier (94) have dealt with the problem of the small myelinated fibers that supply muscle through the ventral roots and what they do, a problem incidentally that has plagued many people for many years. Briefly, in frog muscle, these fibers when stimulated give rise to potentials of the "end-plate potential" type and nonpropagated contractions. Other pertinent data are presented and interpreted with commendable restraint. It would seem most important to establish the function of the supposedly comparable fiber system in mammalia.

Several publications (95 to 98) are concerned with acetylcholine and esterase inhibitors in relation to events at the neuromuscular junction; in particular one notes that in general the action of D.F.P. resembles that of eserine, there being, however, minor discrepancies. Also examined have been the actions of epinephrine (99), calcium ions (100), and desoxycorticosterone acetate treatment in rats maintained on a low potassium diet (101).

LITERATURE CITED

1. Lorente de Nó, R., *A Study of Nerve Physiology*, Part I, No. 131, 496 pp.; Part II, No. 132, 548 pp. (Rockefeller Inst. Med. Res., New York, N. Y., 1947)
2. Lorente de Nó, R., *Harvey Lectures Ser.*, **42**, 43–105 (1947)
3. Grundfest, H., *Ann. Rev. Physiol.*, **9**, 477–506 (1947)
4. Eccles, J. C., *Ann. Rev. Physiol.*, **10**, 93–116 (1948)
5. Fenn, W. O., Cobb, D. M., Hegnauer, A. H., and Marsh, B. S., *Am. J. Physiol.*, **110**, 74–96 (1936)
6. Carlson, F. D., Brink, F., and Bronk, D. W., *Federation Proc.*, **7**, 18 (1948)
7. Connelly, C. M., and Bronk, D. W., *Federation Proc.*, **7**, 22 (1948)
8. Tobias, J. M., *Federation Proc.*, **7**, 124 (1948)
9. Ling, G., *Federation Proc.*, **7**, 72 (1948)
10. Hodgkin, A. L., *J. Physiol. (London)*, **106**, 305–18 (1947)
11. Hodgkin, A. L., *J. Physiol. (London)*, **106**, 319–40 (1947)
12. Hodgkin, A. L., and Huxley, A. F., *J. Physiol. (London)*, **106**, 341–67 (1947)
13. Hodgkin, A. L., *J. Physiol. (London)*, **107**, 165–81 (1948)

[2] A paper by Bullock (102) that appeared as this manuscript was being typed somewhat mitigates the force of this statement.

14. STROHL, A., AND DESGREZ, H., *Compt. rend. soc. biol.*, **142,** 184–85 (1948)
15. BONVALLET, M., ALBE-FESSARD, D., AND FESSARD, A., *Arch. intern. physiol.*, **54,** 119–24 (1946)
16. GÖTHLIN, G. F., AND LÖFGREN, B. L., *Acta Physiol. Scand.*, **15,** 207–29 (1948)
17. EULER, C. v., *Acta Physiol. Scand.*, **15,** 93–99 (1948)
18. GRAHAM, H. T., AND BLAIR, H. A., *J. Gen. Physiol.*, **30,** 493–517 (1947)
19. MONNIER, A. M., *Arch. intern. physiol.*, **54,** 348–71 (1947)
20. BONNET, V., AND MONNIER, A. M., *Arch. intern. physiol.*, **55,** 27–36 (1947)
21. LORENTE DE NÓ, R., AND FENG, T. P., *J. Cellular Comp. Physiol.*, **28,** 397–464 (1946)
22. GALLEGO, A., AND LORENTE DE NÓ, R., *J. Cellular Comp. Physiol.*, **29,** 189–206 (1947)
23. ROTHENBERG, M. A., *Federation Proc.*, **7,** 105–6 (1948)
24. GALLEGO, A., *J. Cellular Comp. Physiol.*, **31,** 97–106 (1948)
25. SHANES, A. M., *Science*, **107,** 679–81 (1948)
26. ENGBAEK, L., *Investigations on the Course and Localization of Magnesium Anesthesia. A Comparison with Ether Anesthesia*, 189 pp. (Busck, Copenhagen, Denmark, 1948)
27. TURNER, R. S., AND FUHRMAN, F. A., *Am. J. Physiol.*, **150,** 325–28 (1947)
28. NACHMANSOHN, D., AND ROTHENBERG, M. A., *Progress in Neurology and Psychiatry*, 59–75 (Grune & Stratton, New York, N. Y., 1946)
29. GERARD, R. W., AND LIBET, B., *Progress in Neurology and Psychiatry*, 26–58 (Grune & Stratton, N. Y., 1946)
30. NACHMANSOHN, D., *Ann. N. Y. Acad. Sci.*, **47,** 395–428 (1946)
31. GERARD, R. W., *Ann. N. Y. Acad. Sci.*, **47,** 575–600 (1946)
32. CRESCITELLI, F., KOELLE, G. B., AND GILMAN, A. J., *J. Neurophysiol.*, **9,** 241–52 (1946)
33. BOYARSKI, L. L., TOBIAS, M., AND GERARD, R. W., *Proc. Soc. Exptl. Biol. Med.*, **64,** 106–8 (1947)
34. FELD, E. A., ROTHENBERG, M. A., AND NACHMANSOHN, D., *Federation Proc.*, **7,** 32 (1948)
35. FELD, E. A., GRUNDFEST, H., NACHMANSOHN, D., AND ROTHENBERG, M. A., *J. Neurophysiol.*, **11,** 125–32 (1948)
36. CHADWICK, L. E., AND HILL, D. L., *J. Neurophysiol.*, **10,** 235–46 (1947)
37. TOMAN, J. E. P., WOODBURY, J. W., AND WOODBURY, L. A., *J. Neurophysiol.*, **10,** 429–41 (1947)
38. LORENTE DE NÓ, R., *J. Cellular Comp. Physiol.*, **24,** 85–97 (1944)
39. TOMAN, J. E. P., *Federation Proc.*, **7,** 125 (1948)
40. BROOKS, V. B., AND RANSMEIER, R. E., *Federation Proc.*, **7,** 15 (1948)
41. LIBET, B., *Federation Proc.*, **7,** 72 (1948)
42. SHARPLES, W., GRUNDFEST, H., AND NACHMANSOHN, D., *Federation Proc.*, **7,** 113 (1948)
43. BEUTNER, R., AND BARNES, T. C., *Federation Proc.*, **7,** 8 (1948)
44. NACHMANSOHN, D., *Trans. Am. Neurol. Assoc.*, **72,** 42–45 (1947)
45. NACHMANSOHN, D., AND ROTHENBERG, M. A., *Federation Proc.*, **7,** 84 (1948)
46. ROTHENBERG, M. A., SPRINGSON, D. B., AND NACHMANSOHN, D., *J. Neurophysiol.*, **11,** 111–16 (1948)

47. BREMER, F., AND TITECA, J., *Arch. intern. physiol.*, **54**, 237–72 (1946)
48. LUNDBERG, A., *Acta Physiol. Scand.*, **15**, Suppl. No. 50, 1–67 (1948)
49. KATZ, B., *J. Physiol. (London)*, **106**, 411–17 (1947)
50. GEETS, W., *Arch. intern. physiol.*, **54**, 372–405 (1947)
51. FESSARD, A., AND MATTHEWS, B. H. C., *J. Physiol. (London)*, **95**, 39p–43p (1939)
52. BARRON, D. A., AND MATTHEWS, B. H. C., *J. Physiol. (London)*, **92**, 276–321 (1938)
53. ECCLES, J. C., *J. Physiol. (London)*, **101**, 465–83 (1943)
54. ECCLES, J. C., *J. Neurophysiol.*, **9**, 87–120 (1946)
55. BROOKS, C. MCC., AND ECCLES, J. C., *J. Neurophysiol.*, **10**, 251–74 (1947)
56. BREMER, F., *Ann. Rev. Physiol.*, **9**, 457–76 (1947)
57. BONNET, V., AND BREMER, F., *Proc. Intern. Physiol. Congr., Oxford, 17th Congr.*, 133–34 (1947)
58. BERNHARD, C. G., *Acta Physiol. Scand.*, **14**(6), Suppl. No. 47, 1–25 (1947)
59. BERNHARD, C. G., AND SKOGLUND, C. R., *Acta Physiol. Scand.*, **14**(7), Suppl. No. 47, 1–12 (1947)
60. SKOGLUND, C. R., *Acta Physiol. Scand.*, **14**(1), Suppl. 47, 1–13 (1947)
61. SKOGLUND, C. R., *Acta Physiol. Scand.*, **14**(2), Suppl. No. 47, 1–16 (1947)
62. BERNHARD, C. G., AND THERMAN, P. O., *Acta Physiol. Scand.*, **14**(3), Suppl. No. 47, 1–10 (1947)
63. BERNHARD, C. G., AND THERMAN, P. O., *Acta. Physiol. Scand.*, **14**(4), Suppl. No. 47, 1–14 (1947)
64. BERNHARD, C. G., AND THERMAN, P. O., *Acta Physiol. Scand.*, **14**(5), Suppl. No. 47, 1–18 (1947)
65. BERNHARD, C. G., SKOGLUND, C. R., AND THERMAN, P. O., *Acta Physiol. Scand.*, **14**(8), Suppl. No. 47, 1–10 (1947)
66. ÅSTRÖM, K. E., *Acta Physiol. Scand.*, **14**(10), Suppl. No. 47, 1–9 (1947)
67. BROOKS, C. MCC., ECCLES, J. C., AND MALCOLM, J. L., *Federation Proc.*, **7**, 15 (1948)
68. LLOYD, D. P. C., AND MCINTYRE, A. K., *Federation Proc.*, **7**, 74 (1948)
69. EULER, C. V., AND SKOGLUND, C. R., *Acta Physiol. Scand.*, **14**(9), Suppl. No. 47, 1–19 (1947)
70. DENNEY-BROWN, D. E., AND LIDDELL, E. G. T., *J. Physiol. (London)*, **63**, 70–80 (1927)
71. BERNHARD, C. G., AND THERMAN, P. O., *Acta Physiol. Scand.*, **13**, 162–66 (1947)
72. TEN CATE, J., WALTER, W. G., AND KOOPMAN, L. J., *J. Neurophysiol.*, **10**, 223–33 (1947)
73. TEN CATE, J., HORSTEN, G. P. M., AND KOOPMAN, L. J., *Arch. intern. physiol.*, **55**, 51–58 (1947)
74. HORSTEN, G. P. M., *Arch. intern. physiol.*, **55**, 304–6 (1948)
75. RENSHAW, B., AND ROSENBAUM, H., *Federation Proc.*, **7**, 100–1 (1948)
76. LETTVIN, J. Y., *Federation Proc.*, **7**, 71 (1948)
77. BRIHAYE, J., *Compt. rend. soc. biol.*, **142**, 261–63 (1948)
78. LORENTE DE NÓ, R., *J. Cellular Comp. Physiol.*, **29**, 207–88 (1947)
79. MCINTYRE, A. K., AND LLOYD, D. P. C., *Federation Proc.*, **7**, 79–80 (1948)

80. SCHOEPFLE, G. M., *J. Neurophysiol.*, **10**, 339–47 (1947)
81. BRONK, D. W., LARRABEE, M. G., AND GAYLOR, J. B., *J. Cellular Comp. Physiol.*, **31**, 193–212 (1948)
82. BROOKS, C. McC., AND ECCLES, J. C., *J. Neurophysiol.*, **10**, 349–60 (1947)
83. BRONK, D. W., BRINK, F., AND LARRABEE, M. G., *Federation Proc.*, **7**, 14 (1948)
84. POSTERNAK, J. M., AND LARRABEE, M. G., *Federation Proc.*, **7**, 96 (1948)
85. FELDBERG, W., AND HEBB, C., *J. Physiol. (London)*, **107**, 210–21 (1948)
86. ECCLES, J. C., *J. Neurophysiol.*, **10**, 197–204 (1947)
87. BRONK, D. W., *J. Neurophysiol.*, **2**, 380–401 (1939)
88. VAN HARREVELD, A., AND FEIGEN, G. A., *J. Neurophysiol.*, **11**, 141–48 (1948)
89. BULLOCK, T. H., *Physiol. Revs.*, **27**, 643–64 (1947)
90. WIERSMA, C. A. G., AND SCHALLEK, W., *J. Neurophysiol.*, **10**, 323–9 (1947)
91. SCHALLEK, W., WIERSMA, C. A. G., AND ALLES, G. A., *Proc. Soc. Exptl. Biol. Med.*, **68**, 174–78 (1948)
92. SCHALLEK, W., AND WIERSMA, C. A. G., *J. Cellular Comp. Physiol.*, **31**, 35–47 (1948)
93. KUFFLER, S. W., AND GERARD, R. W., *J. Neurophysiol.*, **10**, 383–94 (1947)
94. KUFFLER, S. W., LAPORTE, Y., AND RANSMEIER, R. E., *J. Neurophysiol.*, **10**, 395–408 (1947)
95. FILLENZ, M., AND HANAFIN, M., *J. Neurophysiol.*, **10**, 189–95 (1947)
96. BROWN, G. L., BURNS, B. D., AND FELDBERG, W., *J. Physiol. (London)*, **106**, 36P (1947)
97. COPPÉE, G., AND BACQ, Z. M., *Compt. rend. soc. biol.*, **141**, 859–60 (1947)
98. MASLAND, R. L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 544–45 (1947)
99. BROWN, G. L., BÜLBRING, E., AND BURNS, B. D., *J. Physiol. (London)*, **107**, 115–28 (1948)
100. COPPÉE, G., *Arch. intern. physiol.*, **54**, 323–47 (1946)
101. WALKER, S. M., *Am. J. Physiol.*, **150**, 451–60 (1947)
102. BULLOCK, T. H., *J. Neurophysiol.*, **11**, 343–64 (1948)

THE ELECTRICAL ACTIVITY OF THE BRAIN[1]

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Since 1946 publications on electroencephalography (EEG) have appeared at the rate of about one a day. A bibliography has been collated (1) and from this have been selected the papers of greater interest to physiologists.

The development of the subject during the period covered has been almost explosive, both as a routine clinical procedure and as a branch of electrophysiology. There are now many hundreds of EEG departments, and special societies have been founded in Britain, the United States, Denmark, the French speaking countries, and Italy; an international federation of these bodies and an international journal are projected (2). An international meeting was held in London in 1947 and another is planned for Paris in 1949. Some of the societies have issued recommendations and specifications covering equipment, training of workers, and the planning of laboratories (3, 4).

Several useful reviews of various aspects of the subject have appeared. The last in this journal was that by Lennox & Lennox (5); much relevant information is contained also in those of Bremer (6), Grundfest (7), Woolsey (8), McCulloch & Lettvin (9), Eccles (10), Lloyd (11), and Magoun (12) in this *Review*. General and physiological aspects are also considered elsewhere in the articles by Bremer (13), Gibbs (14, 15), Jasper (16), Jasper & Kershman (17), van der Horst (18), Liberson (19), Tavares Bastos (20) and Rémy (21, 22), in all of which the clinical applications of electroencephalography are also discussed. A synopsis in the form of a subject and author index has been compiled by Barnes (23).

An impression of certain already well-defined national characteristics can be obtained from the surveys of Baudouin (24), Delay & Verdeaux (25), Frey (26), Kornmüller (27, 28), and Walter (29), and a brief survey of the history of the EEG in the service of the clinician is given by Cobb (30). Most aspects are considered in the first book devoted entirely to the subject (31).

The most important fundamental advance is that, after twenty

[1] This review covers the period from June, 1946 to June, 1948.

years, empirical and statistical studies are giving place to inductive, analytical, and experimental ones [Carmichael (2)]. To some observers it appears that a new branch of science is developing from the study of the brain as a transformer and transmitter of signals; as yet unnamed, this subject could be described as neurosemantics.

Technical Advances

Recording systems.—While the growth-curve of circuit complexity seems to be flattening, with efforts directed mainly towards elimination of batteries and compactness (2, 32 to 35), several new varieties of recorder have been described (2, 35). Some improvements have been achieved in amplitude, fidelity, and robustness, but only the "capstan" model designed by Matthews (36) is really novel and holds promise of direct recording up to the order of kilocycles per second.

Multichannel systems are now commonplace, six or eight being preferred. A logical development of this tendency has been described by Walter (2) as a toposcope. In this instrument the electrical activity of the various brain areas is picked up by fifty or more channels and displayed on the screen of a cathode-ray oscilloscope as a pattern of flashing light-spots corresponding to the topographic arrangement of the electrodes on the brain or head. Some such system may be essential for accurate spatial analysis in the application of experimental methods to human subjects. A trend in the opposite direction is exemplified by a further method of converting the output of a single channel into audible sounds (37). More than a dozen commercial electroencephalographs are now in production. It has been observed that their merit is an inverse function of the extent of their advertisement (38). Bagchi & Bassett (39) claim improved accuracy of location with a "three dimensional" system employing successive or simultaneous records from the ear to scalp, scalp to scalp, and nose to scalp. Cohn (40) has used a three-gun cathode-ray oscilloscope to facilitate comparison of phase relations in detailed studies of alpha activity. Methods of overcoming the special difficulties in recording from young children are suggested by Barnes & Amoroso (41), who recommend the use of pentothal, and Laplane, Fischgold & Brisac (42), who also encourage sleep with sedatives. Recording during sleep is claimed by the Gibbs to increase the proportion of abnormal records in epileptics (43, 44).

The weakest link in the technical chain is still the electrode system. The inconvenience of present designs, emphasised by multiplication of recording channels, is reduced to absurdity by attempts at toposcopic display. Even the electrochemistry of the electrode metal is still a mystery to many though recommendations on this subject are clear and timely (3). The pattern of electrode placement has also been studied and reported on (3). The impossibility of achieving a true "unipolar" system on the head has been established and the practise of commoning one side of all channels to the ears is becoming unfashionable. Several new methods of attachment have been described (45 to 48), special electrodes have been used for the direct exploration of subcortical structures in man (49, 50) and pharyngeal electrodes for the study of basal activity (51, 52, 53). A simple but important improvement on the pad and pressure type of electrode is due to Rémond (54). This consists of a wide low tripod with silver-silver chloride pads on each foot; three electrodes are thus held on with a single band at equal pressure, five or six such tripods providing all the usual positions. Further improvements are required to give the speed, comfort, and flexibility essential in prolonged experiments.

Analysis of records.—The inadequacy of the unaided eye in interpreting complex curves becomes more obvious as interest shifts from the superficial to the detailed features of the records. Methods of manual analysis have been discussed by Engel & Hoagland (55).

The automatic analyser designed by Baldock & Walter (56) is in use in several centres and another method of obtaining a frequency analysis superimposed automatically on the primary trace has been developed by Barbour (57). This latter has the disadvantage that the chance of a given component being included in the analysis depends upon the moment at which it occurs in the primary trace, since the frequency of the selective circuit is swung through the gamut of frequencies every four seconds at a rate of five cycles per second in the middle range and a bandwidth of one cycle.

The value of frequency analysis has been questioned by Gibbs & Grass (58), who fear that the spectral display may distract attention from the primary trace. The importance of regarding the records from the various channels and their analyses as a whole picture has been emphasised by Bugnard (59) and Walter *et al.*

(2, 31, 60). The analysis should be used to direct attention to hidden qualitative features of the record as well as to measure them. It has also been pointed out that by separating the various components in frequency analysis the activities of individual cell groups may be identified, so that frequency analysis is linked with spatial, topographic, and anatomical analysis. Resolution power is further increased by using an analyser as an interchannel phase-discriminating device; even without frequency separation, phase analysis can be helpful in location studies, as in the arrangement devised by Sonnemann & Kennard (61).

Some elementary theoretical aspects of wave synthesis and analysis in the interpretation of EEG records are considered by Gualtierotti (62, 63), who stresses the composite nature of most rhythmic activity. Bertrand & Lacape (64) have developed a quite elaborate harmonic theory of brain rhythms based on mathematical analyses of isolated bursts or "spindles" of waves. The ingenuousness of these ideas is probably due to the mediocrity of the records studied by Lacape, whose untimely death prevented him from handling more significant data. Examples of the misconceptions prevalent in many minds are presented by Boyd (65). An excellent treatment of the analysis and synthesis of EEG patterns is due to Rémy (66). The recognition of artefacts is still a major problem in human studies, and methods for reducing or objectifying them have been suggested (67, 68). The more elaborate the technique, the more subtle and elusive the artefacts. Walter (2, 31, 60) has pointed out that not only is an automatic analyser incapable of discriminating against artefacts but it can also introduce spurious harmonic components if the EEG amplifiers are overloaded or unbalanced. Further, although such an instrument permits measurement of rhythmic components a hundred times smaller than the average noise or interference background, it cannot be expected to indicate whether these components are real or whether they are due to modulation or to inherent limitation of potential change by physiological constraints. It is still necessary to employ every stratagem to locate and delimit the phenomena under investigation. The general truth must be accepted, that operation on a message may translate it into a more tractable, intelligible language but can never add to the information it contains and may adulterate it with irrelevant and bewildering distortions.

An important general tendency is toward the correlation of the

EEG data with other physiological variables such as peripheral stimuli, muscular activity, and autonomic changes. This healthy development is a feature of purely clinical, as well as physiological, studies and implies a higher level of technical competence and a wider background on the part of both research workers and technicians. Special techniques have been developed for the registration of peripheral phemonena by Darrow (69, 70, 71) and by Hill *et al.* (72).

Combination of human electroencephalography with peripheral stimulation also requires some special precautions and devices. Dawson, for example (73), describes a series of control experiments and a special recording technique to obtain clear records of brain activity when using a high amplification during electrical stimulation of the peripheral nerves. Walter, Dovey & Shipton (74) demonstrated the value of an oscillator-controlled electronic flash-generator in the study of the electrical response to photic stimulation. This system has the unique advantage that with a suitable trigger circuit the stimulus can be accurately synchronised with any desired phase of the spontaneous rhythms or evoked response to provide positive or negative feedback, resulting in oscillatory, convulsive, or ultrastable cerebral conditions.

Physiological Mechanisms

The classical division between animal and human experiments seem less profitable than heretofore. There is, however, a difference between experiments intended to elucidate the nature and function of the electrical phenomena in the brain and those in which records of these phenomena are used to detect, test, or assay some other variable. For the purposes of this review this section includes mainly observations in the former class.

Spontaneous activity.—The term spontaneous should perhaps be quoted, for it is difficult to prove in the case of an organ so specialised for storage and memory as the brain, that apparently spontaneous activity is not the indefinitely prolonged after-effect of some previous experience. The term should therefore be taken to embrace those electrical events which are not obviously caused by changes occurring at the time of the experiment. The prototype in this category, the alpha rhythm, has been seen by every electroencephalographer but studied specifically by surprisingly few. There is still no agreement as to its relation to axon and neurone poten-

tials, to chemical or autonomic changes, or to physiological and psychological function. One notable advance is that the wider use of location techniques has established the view that alpha activity as ordinarily recorded is complex, polyrhythmic, parietooccipitally located and merely a representative of many smaller rhythms in other areas [Adrian (75), Bremer (13), Cohn (40), Dubouloz, Gastaut & Corriol (2), Walter *et al.* (2, 31)].

There are four main points of view on the generation and function of the alpha class of electrical activity. Adrian (75) considers that the regular sinusoidal alpha rhythm of rest is due to the fortuitous synchronisation of large groups of cortical neurones, while the blocking effect of peripheral stimuli he attributes to the unequal acceleration and intensification of activity of the same cells by the unsynchronised heterogenous centripetal impulse volleys. Bremer (13) goes further, believing that all the spontaneous resting rhythms are composed of axon potential volleys superimposed upon rhythmic synchronised fluctuations of neuronic membrane potentials. He explains the blocking effect of stimuli as an acceleration of the discharge rate in the projection areas and a partial desynchronisation in the nearby regions. Speculatively, he accords these resting rhythms the function of maintaining an incessant alternation of excitation and inhibition, reminiscent of the "hunting" exhibited by a crude servo-device. McCulloch and his associates (76, 77) and Walter (2) have suggested that these rhythms may have a more subtle function, that of scanning the projection areas for information. On this hypothesis, the alpha rhythm of the visual areas is supposed to sweep over the projection zone, perhaps the association areas as well, in a systematic raster so as to pick up and reflect the spatial pattern of activity projected from the receptor. In this way a spatially displayed apparition would be coded into a series of signals on a time base for transmission and decoding, rather as in a television system. From the design and production standpoint, such a device would have the advantage of compactness and the capacity rapidly to transform and compare a large number of exogenous and endogenous signals. The presence of several components in the alpha rhythm suggests the possibility of interlaced scanning, possibly connected with such psychological functions as recognition and recall. One virtue of this scheme is that it demands synchronisation of the resting rhythms over a wide area of cortex and thalamus as a functional necessity, instead

of dismissing this feature as a coincidence. The blocking reaction is inevitable in such a system since the sweep is supposed to be stopped when it encounters a region of activity. A photoelectronic model with these properties has been described by Walter (2). Quite a different attitude is adopted by Darrow (69, 78), who regards the alpha rhythm as a cause rather than a consequence of repose. He describes the corticothalamocortical feedback pathways as a governor or escapement system whereby cortical function is limited to a burst of activity at every half-cycle and suggests that prolonged alpha activity may cause cerebral vasoconstriction indirectly by reducing metabolism. These various hypotheses are surprisingly difficult to understand in detail; they all suggest experiments and provide excellent exercises for logical and semantic analysis; they are not incompatible.

The long overdue theoretic fertility evidenced by these notions suggests that the philosophical implications should not be ignored. The presence of "spontaneous" rhythmic activity of the alpha type is predicted by several modern theories of purposive and adaptive behaviour. Ashby (79 to 82) points out that the automatic development of equilibrium in self-organizing systems depends upon their containing variables which are step- and part-functions of time, and Rosenblueth and others (83) also have argued that the presence of purposive or goal-seeking behaviour is not diagnostic of life, since modern error-operated servo-devices with negative feed-back circuits also display this character. In such systems, oscillations of certain variables in an alpha fashion may have hunting, scanning, discriminating, limiting, and storage functions. In spite of their intricacy and suggestiveness these ideas do not throw light on the physical basis of spontaneous activity. There is ample evidence that, in conditions of extreme excitability, electrical discharges in brain and spinal cord can spread over wide areas independently of anatomical pathways [Bremer & Colle (2)], presumably by simple physical spread of electrical fields, and in these conditions synchronisation and rhythmicity are most prominent. The physiological alpha-like rhythms are not very large, however, and transection of corticothalamic connections usually abolishes or greatly modifies the rhythm while stimulation of basal structures produces prolonged rhythmic discharges from most areas of the cortex in anaesthetised animals (2, 84, 85). Most workers invoke a diencephalic regulating centre to explain the

properties of the rhythmic discharges. Margaria (86) has observed that in man the discharge frequency of a single motor unit is 10 to 18 per sec. during voluntary contraction and does not vary with the tension exerted. The classical opposite finding he attributes to the use of overlarge electrodes with inclusion of many motor units. He studied also the activity of the higher motor neurones in cats, using the technique developed by Gualtierotti *et al.* (87, 88) of progressive electronarcosis of the diencephalon to reveal single-unit discharges. He found that, for up to one minute after electrical inhibition of this type, regular waves at 10 to 18 cycles per sec. appear in the motor cortex. These are often accompanied by single spikes, always on the same phase of the wave. Margaria suggested that these slow waves result from the propagation of an impulse through a controlling neurone circuit having an over-all delay of 1/10 to 1/18 sec., the spikes being the manifestation of a single element in a subcircuit with effector functions, the other elements of which are suppressed by the diencephalic inhibition. He considers that spontaneous activity in other regions, including the alpha rhythm and abnormal rhythms, may have a similar explanation. Since Sperry (89) has shown that shallow criss-cross incisions in the sensorimotor cortex do not abolish motor co-ordination, it seems unlikely that superficial cortical circuits are involved in functional integration but there is no particular reason why both triggering from undifferentiated thalamic nuclei and local field effects should not participate in a reverberatory or retroactive fashion.

Suppression of activity.—Possibly in a different category from alpha-blocking is the suppression of cortical activity by various types of stimulus. Leão (90) has continued his study of the electrical depression which spreads slowly over the cortex from the neighbourhood of a stimulated area. He finds this is accompanied by a slow potential change of the order of 10 mv. negative for 1 to 2 min., positive and smaller for 3 to 5 min. A similar slow negative variation occurs after prolonged asphyxia and Leão suggests that the spreading depression is associated with some change similar to that due to anaemia.

Gerebtzoff (91) has reported that in rabbits and Bremerised cats, hypnosis or catalepsy induced by rapid inversion produces a suppression of electrical activity, with reduction in the size of responses evoked by receptor or electrical stimulation, the after-dis-

charge of these being particularly attenuated. Immobility induced in other ways is associated with large, slow, sleep-like waves. These effects are attributed to inhibition from basal nuclei. Gualtierotti and his associates (87, 88) claim that stimulation of the cortex or diencephalon with square pulses at a frequency of 280 cycles per sec. results in suppression of electrical activity over a wide area for some minutes after the end of the stimulus. Motor function and consciousness are also impaired during this period.

The discovery of several extensive suppressor areas such as 2, 4s, 8, 19, and 24 and their elaborate connections (92) introduces the possibility of suppression of activity in suppressor areas, a bewildering but inevitable complication. Gellhorn & Ballin (93) found that nociceptive impulses from the periphery alter both cortical and hypothalamic activity in the same way; weak stimuli suppressed the Dial waves, stronger ones increased the background frequency, maximal excitation increased both frequency and amplitude of the background activity. It is suggested that these effects are due to synchronisation at first, followed by recruitment at higher excitation levels. In later experiments, Gellhorn (94) found that in similar conditions the suppressor areas, as well as the sensorimotor and projection ones, are excited and surmises that the former may participate in a homeostatic function. Barker & Gellhorn (95) found that stimulation of the suppressor areas in the cat diminished not only the spontaneous activity but also the size of the responses evoked by afferent stimulation in the receptor fields.

Failure to detect potential changes may be due to their true absence or to their complete randomisation, which latter may be equivalent to maximal functional activity. In experiments such as these it is imperative to compare the records with control ones taken with the recording electrodes on a dead brain or in a physiological saline solution presenting a resistance comparable with that of the preparation. Comparison of the noise level of the two records is essential before any assertion can be made as to the presence or absence of activity.

Continuing their studies of depression induced by local application of acetylcholine, Forster, Borkowski & McCarter (96) report that this effect, like that of Leão, does not follow anatomical pathways and is accompanied by decreased cortical responsiveness. Although depression occurs before acetylcholine discharges, the latter do not always follow when the acetylcholine solution is weak

and, moreover, remain localized or spread by anatomical routes.

Subcortical activity.—Spontaneous activity in deeper nuclei is as complex as in the cortex, but the extent to which it is visible with indirect leads is doubtful. Observations made with a single nasal or pharyngeal electrode (51, 53, 97) are inconclusive, since the distance to basal structures is not much less than with mastoid electrodes, and when the pharyngeal electrode is referred to the ears, quite misleading similarities between "basal" and "cortical" records occur. A bipolar electrode as described by Gastaut (52) is more trustworthy, since it is important to discriminate between these components which are and those which are not common to cortex and base. Records taken with small insulated electrodes introduced through the overlying structures in unanesthetised subjects suggest that the resemblance between the cortical and basal activity is less complete than was imagined, though the larger rhythms such as the alpha are certainly present in parts of the thalamus and hypothalamus.

Evoked potential changes.—The electrical response of the various parts of the brain to stimulation of sense organs and other regions has long been used for physiological mapping of anatomical pathways in animals. This work continues (98 to 102), but the results are not always easy to interpret because electrical activity is not synonymous with functional activity; electrical activation of one region by another or by sensory stimulation implies a connection between the two but does not prove whether the action is functionally positive or negative. Furthermore, the nature of the stimulus may have a profound effect upon the response (103, 104). Strychninisation of the brains of animals immobilised by anaesthetics may have misleading results since the frequency of discharge is usually far from physiological and the effect of the anaesthetic may include diversion of signals from effector pathways.

The difficulties of recording from human subjects, reduced by modern methods, are outweighed by the gain from having normal brain and subjective reports (74, 105, 106, 107). Photic stimulation is the handiest tool for studying evoked responses in man. These are usually large enough (up to 50 μv) to measure directly, always clearly revealed by analysis (74, 105, 107). Livanov & Poliakov (108) have pointed out that rhythmic stimulation combined with mathematical frequency analysis of records provides enhanced resolution of response detail, and this has been confirmed with

automatic analysis (74, 107) which permits location and measurement of evoked responses at a level of 0.01 μv. Responses to photic stimulation do not appear to be "driving the alpha rhythm" since, with the eyes shut, activity at both stimulus and alpha frequency exist together and appear as beats in the primary records, separate components in analysis. Considering the frequency stability and relative purity of the alpha rhythm in most subjects, the selectivity or "Q" of the alpha mechanism is surprisingly low if there is a true resonance effect. There is, however, a true interaction between flicker responses and certain components of the alpha rhythm in some subjects, and with other rhythms for example, the theta rhythm in children and certain types of normal adult. In most subjects, voluntary mental activity involving visual imagery reduces the amplitude of the occipital components of the evoked response, as well as that of the alpha rhythm; the form, harmonic content, and topography of the response are also modified to a variable extent. Subjective sensations associated with flicker include pulsating mosaics, whirlpools, kinaesthetic hallucinations, and organised delusional states. The simpler hallucinations are attributed to stroboscopic visualisation of the alpha scanning field by the intermittent stimulation. The more elaborate ones are associated with electrical activity in fundamental, harmonic, or subharmonic modes in the related cortical zones. The variation between individuals and in the same subject from time to time is considerable; there are intricate correlations with maturity, psychological type and mood, as well as with wakefulness, the action of drugs, and clinical conditions, summarised below. On the borderline between physiology and pathology is the induction of epileptic seizures by photic (and auditory) stimulation at critical frequencies (74, 107, 109). Electronic triggering of the stimulus by the evoked response has interesting possibilities. The response wave is selectively filtered, squared, differentiated, clipped, and rectified, then applied to an integrating circuit with controllable characteristics, to provide adjustable phase relations between response and stimulus independently of amplitude and repetition rate. Data so far obtained appear to confirm the existence of sweep circuits in visual cortex, with wide variations between individuals.

The latency of the evoked response is a better measure of "central time" than is the blocking of the alpha rhythm (110). It is obtained by measuring the interval between the rise of the B-

wave of the ERG and the rise of the surface-positive wave of the EEG response and varies from 35 to 65 msec., while the alpha blocking time is still more variable, indeterminate and may be absent entirely.

The form of the cortical response to a single brief light stimulus in man is a surface positive saw-tooth wave located in the projection area, followed by a variable number of oscillations, some of which appear also in secondary receptive fields [Walter & Walter (107)]. The dipole equivalent to the primary response is orientated radially, whereas that corresponding to the secondary waves has a variable orientation. With rhythmic stimulation the secondary waves can be detected in areas even more remote from the projection field and are represented in analysis as components numerically related to the stimulus frequency.

Auditory stimulation evokes small but detectable responses in the temporal region in man, provided that the sound is loud and steep-fronted so as to excite the majority of the cochlear resonators (105, 111).

Dawson (73) has studied the cortical response to electrical stimulation of sensory nerves in man. He finds that in most clinically normal subjects a strictly focal cortical response appears in the contralateral sensory area, near the midline from leg stimuli, further laterally from arm. The amplitude is only of the order of 10 μv, surface positive, followed by smaller possibly more diffuse oscillations. The latency with stimulation at elbow is about 20 msec., at knee about 35 msec. When two successive stimuli were supplied at an interval of 70 to 100 msec., the subjects reported an alteration in the quality of the sensation, absent at longer or shorter intervals.

Livanov & Poliakov (108) claim that the formation of a conditioned reflex to rhythmic stimuli can be followed in the change of electrical pattern in the cortex of an unanaesthetised rabbit. Their records are not particularly convincing but are said to show that during the generalisation phase of the conditioning, activity at the frequency of the conditioned stimulus spreads from the projection zone to nearly all areas, then settles down in the effector field corresponding to the unconditioned response, at which stage the conditioned reflex proper appears. It is alleged that all the features of Pavlovian conditioning can be followed in this way.

Corticobasal relations.—The interrelations of different brain

areas are as intricate as could be imagined; interest has centered mainly on the connection between basal structures and cortex. McCulloch, Graf & Magoun (100) found that strychninisation of area 4s in monkey evokes activity in a pathway diverging from the corticospinal tract in the pons to the bulbar-reticular formation. They consider this may be an extrapyramidal system mediating relaxation. Ward & McCulloch (98) discovered discrete projections from area 6a to the mammillary bodies, lateral hypothalamus, and posterior hypothalamus, which latter also receives from the orbital cortex. Other frontal areas transmit to the supraoptic and paraventricular nuclei. Delgado & Livingston (112) have shown that electrical stimulation of orbital cortex produces a wide variety of autonomic effects, the detail depending upon the frequency and intensity of the stimulus—an important phenomenon which cannot be studied by strychninisation. Ward (99) has observed marked autonomic effects and suppression of electrical, motor, and reflex activity during stimulation of the cingular area 24.

Droogleever-Fortuyn & Jasper (2, 84, 85) stimulated the thalamus electrically in anaesthetised cats, recording simultaneously from six cortical areas. Generalised bursts of slow waves, appearing first in frontal, later in posterior regions, were evoked by stimulation near the midline in the dorsomedial nucleus. Stimulus frequency was critical; when synchronised with that of the cortical response, marked augmentation occurred, especially in the anterior regions, which could be driven into wave and spike activity resembling that seen during human *petit-mal* when the frequency was about 3 cycles per sec. In later experiments with unanaesthetised animals, this procedure produced behaviour changes also resembling *petit-mal*.

Walter & Walter (107) have induced myoclonic seizures in patients with epilepsy by photic stimulation. Measurements of the time relations of the various evoked responses suggest that leakage is occurring direct from the external geniculates through the pulvinar to the dorsomedial nucleus, thence simultaneously to the frontal cortex and musculature. Since these effects were particularly distinct in twins suffering from Unverricht's familial myoclonus (113), the cross-firing may be due to a genetic anomaly affecting the insulation of the corticothalamic circuits from afferent channels.

In all these experiments the critical relation between the frequencies of spontaneous oscillations and stimulus is most striking; the selectivity of the cerebral circuits often seems much higher than would be expected from the rate of increment and decrement on starting and stopping the stimulus, if the latter were driving a simple feed-back resonating circuit. Inconsistency between these parameters suggests that the circuits are not simple ones, but contain variables which are step-functions of time.

Biochemistry, Pharmacology, and Metabolism

The EEG has not so far proved a very sensitive or discriminating method of studying biochemical effects. Engel, Webb & Ferris (114) found similar changes in men submitted to anoxia equivalent to altitudes of 10,000 ft., alcoholic intoxication, and hypoglycaemia; a shift towards the low frequencies was the main alteration in all cases. Similar observations were made by Finesinger *et al.* (115). Gellhorn & Ballin (116) obtained similar results in rats intoxicated with water, with the addition of spikes at various stages of hydration; in animals treated with desoxycorticosterone acetate only slow waves appeared. The generality and nonspecificity of the slow waves and spikes suggested that the similar patterns seen in human epileptics are due to the same basic disturbance of cerebral function. This inference is supported by the observation of Swinyard, Toman & Goodman (117) that in rats cellular hydration lowers and dehydration raises the threshold for electrically and chemically induced convulsions independently of changes in volume of extracellular fluid. Grenell & McCawley (118) investigated the protective action of adrenal cortex extracts on brain damaged by exposure and concussion; they found the lower frequencies suppressed by the hormone which also prevented edema and staining by trypan blue in the damaged regions. Desoxycorticosterone acetate was less effective and produced some slow waves by itself, whereas the natural extract tended to raise both frequency and amplitude. Van Harreveld (119) examined the effects of asphyxia lasting ten to thirty minutes induced in anaesthetised cats by raising the intradural pressure. Electrical activity generally disappears 10 to 15 secs. after the application of pressure, but some irregular slow activity may persist. After 10 to 15 min. of asphyxia the principal sign of recovery is bursts of activity at 7 to 12 cycles per sec. lasting 1 or 2 secs., 10 to 20 times per min.

These are probably local and cortical. After longer asphyxia, spindles at 12 to 16 cycles per sec. appear at varying intervals. These last 10 to 20 secs. and may have a subcortical origin.

Brazier (120) used interchannel phase-discriminating automatic analysis to sort out the effects of hypoxia, hypoglycaemia, fainting, and pentothal in normal humans. Breathing 8.5 per cent oxygen progressively lowers the alpha frequency to about 6 cycles per sec. when it is still blocked by opening the eyes. A few breaths of air restore normal conditions. The effects of hypoglycaemia are similar, but during a faint the alpha rhythms vanish and are replaced by activity at 2 to 3 cycles per sec. During pentothal anaesthesia the picture is again different, with fast activity in the early stages giving way to a mélange of rhythms during unconsciousness, with a tendency to harmonic grouping. Brazier considers that the ". . . frequency changes caused by oxygen lack and low blood sugar level are changes in the same neuronal population rather than a replacement by activity from other cell units." The effects of pentothal and syncope are interestingly discussed.

While the battle between humoral and electrical hypotheses for possession of the approaches to the brain rages unabated (121, 122, 123), within the cranium only skirmishes have taken place. Bornstein (124) found abnormal amounts of acetylcholine in the cerebrospinal fluid of traumatised brains in cats and dogs, whose EEG's showed both intense activity and transient flattening followed by prolonged abnormal discharges. These abnormalities, and the disturbance of behaviour which accompanied them, could be abolished by atropine, mimicked by perfusion or cisternal injections of acetylcholine, suggesting a humoral factor in the production of traumatic symptoms.

No one would deny that acetylcholine is a very active substance both in oil-water models (125, 126, 127) and in nervous tissue, and even the most intransigeant and humourless neurophysiologist must accord to this group of substances a role at least as important as that of the chemicals in a Leclanché cell; there is no evidence that the electric energy in nerve cells is generated by electromagnetic induction or the accumulation of static charge. However, there seems little profit in arguing whether a flashlamp is an electrical or chemical device; it is more electrical than an oil-lamp, more chemical than a lightning flash and the nervous system probably falls into the same category. A helpful review of the role

of acetylcholine in nervous action has been published by Whitteridge (123).

The clinical value of drugs is often limited by their effects upon the brain and the EEG is useful in studying this. The convulsant action of antibiotics has been studied by Johnson *et al.* (128), Johnson & Walker (129), Suckle, Liebenow & Orth (130), and Borkowski & Forster (131). Engel, Romano & Ferris (132) examined five normal adults under the influence of quinacrine; they found pronounced psychological stimulation and a shift of the EEG towards a higher frequency, with a lag of three days after exhibition. Recovery was delayed even longer after withdrawal. Crescitelli & Gilman (133) observed the effects of DDT emulsions injected into cats and monkeys; the phase relations of the cerebral and cerebellar discharges suggested action in another unidentified structure. Haymaker, Ginzler & Ferguson (134) found cerebellar lesions in dogs after prolonged poisoning with DDT. Engel, Romano & Goldman (135) investigated a case of acute encephalopathy during arsenical treatment; they found only an apparent shift in alpha frequency from 11.5 to 9.1 cycles per sec. with rare waves at 7 cycles per sec. at the height of the reaction. The records suggest that automatic analysis would be of assistance in interpretation, since there are many components present, some masked by larger rhythms. The convulsant effect upon dogs of bleached flour has the expected EEG correlates according to Newell & Erickson (136). Silver *et al.* (137) found slow waves and isolated spikes five minutes after injection of amino acids equivalent to agenised gliadin. Later there were complete *grand-mal* patterns. During feeding with bleached flour there were slow irregular waves, then slow spikes and waves. Cysteine hydrochloride alone produced similar effects. Ward (138) found that intravenous injections of sodium fluoroacetate into cats evoked local cortical and subcortical rhythmic seizure discharges after two hours of depression. These are associated with tonic seizures, but cortex and deeper structures are not synchronised. Wave and spike activity in cortex was sometimes associated with a high-frequency discharge in the thalamus, modulation of which followed the cortical rhythm.

The action of convulsant drugs has been studied by many workers. Toman *et al.* (139, 140) observed that the effect of barbiturates, hydantoinate, and tridione was to abolish the tonic

phase of maximal seizures induced electrically in animals, while glutamic acid did not. Perlstein (141, 142, 143) found that the beneficial effect of tridione in cases with *petit-mal* was mirrored in their EEG's and suggested that the drug acted upon some regions of the midbrain and basal ganglia, an inference supported by study of seizures induced by physiological stimulation. New drugs of value in epilepsy have been surveyed by Gibbs (144), and Lennox (145, 146, 147). Proctor (148) found that patients with records containing marked activity at the harmonics of the alpha rhythm, whatever their complaints, were frequently improved by hydantoinate. Walker & Kirkpatrick (149) also claim good results in ten children with behaviour disorders and abnormal records, and Barnes (127, 150) states that anticonvulsants have a stabilising action on oil-water boundary potentials. Girden (151) observed no effect from curare on the brain and suggests that previous reports to the contrary (152, 153) were due to failure to control the artificial respiration correctly. Tyler (154) studied the effects of amphetamine and barbiturates on the electrical and psychological activity of normal subjects during prolonged wakefulness; slight changes in frequency were the only physiological effect.

Heredity and Development

Genetic factors.—No experiments have been reported on individual EEG variations in animals; consequently experimental genetic studies have yet to be made and human genetics is a notoriously difficult subject, particularly when there are few firm experimental facts. The similarity of the EEG's of monozygotic twins and the constancy of the individual's records indicate a large hereditary factor in determining the details of the electrical pattern. However, analysis reveals that even in identical twins there are small differences in such features as the extent to which the various alpha components respond to mental and physical stimuli (107) and the details of the response to photic stimulation. The magnitude of the differences is slightly larger than the variation from time to time in one of the twins. In neurological conditions with known genetic factors, the EEG abnormalities generally exhibit marked similarities in individuals of an affected family (2, 113, 155). The situation in epilepsy is more complex. Lennox (147) asserts that "the electroencephalogram is an hereditary trait" but admits that it is "fluid." He suggested that in most epileptics both

genetic and acquired factors exist and proposes that these two adjectives should replace "essential" and "symptomatic." Genetic EEG factors in psychiatric disorders are even harder to assess. Gottlieb *et al.* (156, 157) found similarities in the EEGs of parents and children with primary behaviour disorders. The need for a sliding scale of abnormality criteria in comparing parents with children, the difficulty in subjecting qualitative EEG data to rigorous statistical analysis, and the rarity of complete family studies, all these limit the scope and value of work reported so far.

Age and maturation.—Normal children's records show great variability both between individuals in the same age group and at certain ages in the same child from day to day (31, 158, 159). There is evidence of abrupt as well as gradual changes. Some infants show normal alpha rhythms as well as large slow components. Emotional stimulation has a marked effect upon the theta rhythm in many children aged between one and five. Photic stimulation accentuates age differences (44, 74). Understanding of these facts will be incomplete until more is known of the course and variation of neuroanatomical development in humans (160); in animals the electrical development in young coincides with stages of neuronal and axonal maturation (161). In the meantime children's records must be interpreted with some reserve, using a generously weighted scale of criteria (42, 162 to 165). In older patients, successive examinations are always of value; physiological changes are minimal after the age of twenty, when gross variations are suggestive of organic pathology (2, 166, 167).

Sleep, fatigue, and emotion.—Additions to the classical description of EEG changes during sleep suggest considerable individual variations particularly in psychotic patients (2, 168, 169). Insomnia and fatigue produce measurable effects similar to those of alertness (170, 171) which can be influenced to some extent by amphetamine (154). Dynes (172) found no EEG changes in hypnosis which he therefore considers not a sleep variant, whatever else it may be. In coma, auditory arousal stimuli induce greater changes than when the subject is awake (173) suggesting that the brain is behaving more like the reflex system of lower levels. Cohn (174) reports that subjects in hyperemotional states show random low-potential high-frequency activity which is reduced by reassurance and also more rhythmic frontal activity at about 20 cycles

per sec. which is unaffected by stimuli or comforting and is often associated with somatic complaints suggestive of frontal lobe hyperfunction. Some of the central nervous factors connected with pain are discussed by Adrian (175). From study of peripheral neuroanatomy of pain fibres, Weddell *et al.* (176) suggest that "unpleasant" pain after trauma may be due to a simplification of the centripetal impulse pattern leading to delay and re-routing of signals, in the same way as frequency and rhythm control the motor effects of central stimulation.

Pathology

Trauma.—Experimental concussion produces a transient decrease in brain reactance (177). The relation between EEG changes and histopathology has been investigated by Zimmerman & Putnam (178). Ward & Clark (179) produced concussive effects by impact on a plunger in a saline-filled tube leading to the intracranial cavity in animals. The EEG changes were transient and not specific. They found some of the slow components were synchronous with the pulse. Impact to the body of animals had no such effect. The origin and significance of the slow rhythms are interestingly discussed.

In man there has been less opportunity for examining acute trauma. Several reports on chronic cases have been issued (180 to 187). All agree that in the absence of epilepsy or haematoma, most trauma records become normal within a period of months. A persistent abnormality indicates a complication and warns of possible fits. Normal records with persistent complaints or disabilities suggest atrophy, but may be evidence of a psychiatric disturbance. Murphy & Garvin (188) report observations on nine cases of porencephaly. In four true porencephalies the main feature was a lower amplitude of all components on the affected side. In three post-traumatic cases there was a focal slow discharge near the lesion; the presence of phase-reversals in the allegedly unipolar published records casts doubt on some of the interpretations.

Expanding lesions.—There have been numerous reports on the accuracy of location of cerebral tumours (189 to 199). This varies from 65 per cent to 85 per cent according to the technique (excluding methods of activation or stimulation). Bipolar scalp electrode placements are more accurate than attempts at unipolar leads. Electroencephalography is as accurate as any other method alone.

Success is not so great in deeper lesions, where the abnormalities are more subtle, transient, and easily masked by normal features. The occurrence of activity at 4 to 7 cycles per sec. (theta rhythm) when structures around the third ventricle are involved has been confirmed (2, 200). Laufer (201) considers that some subcortical lesions may suppress cortical activity by interruption of cortico-thalamocortical circuits.

In all cases of organic disturbance, the course of evolution of the abnormalities is an important indication of the nature of the lesion (202). Special aspects of these problems have been considered (2, 203 to 206) and Walter, Hill & Williams (207) have discussed many of the features in the EEG due to organic disease. Walter prefers not to dismiss the positive correlation of slow delta waves with diseased brain as adventitious and suggests that slow oscillations may have a function analogous to that proposed by Darrow (78) for the alpha rhythm, that of limiting or constraining the activity of threatened neurones, as a substitute for the mechanisms of pain, lymphatic drainage, and repair possessed by peripheral but denied to central nervous tissue. The soporific effects of very low-frequency sine-wave stimulation on the human brain are quoted in support of this hypothesis. Photic stimulation has been used (207, 208) to trace the extent of lesions in the visual pathways and parietooccipital cortex. Not only can the level of a lesion be inferred by the distribution of evoked potentials; the presence of a slight cortical disturbance is often accompanied by an anomalous dispersion of harmonics in areas remote from the projection zones, even when there is neither positive abnormality nor disturbance of the normal rhythms in the resting records.

Epilepsy.—During the last two years more than one hundred papers have appeared on various aspects of the EEG in epilepsy. Some have been referred to in other sections, but only a few of those with some general or physiological interest can be included in this place.

Statistical reports continue to appear (163, 166, 184, 209 to 215). The proportion of abnormal records remains below 80 per cent in most series, and the insignificance of negative findings is emphasised, while the appearance of apparently epileptic abnormalities in patients without personal or family history of seizures is perplexing (148, 200, 218, 219, 220). The value of the EEG in detecting early cases of epilepsy in children is stressed by Laplane *et al.* (221) and Escardo & Mosovich (222); its value of following

the effects of lowering blood pressure in eclampsia by Whiteacre, Loeb & Chin (223). Findings in several interesting cases have been described (113, 224, 225, 226). Measurements of frequency and amplitude are not sufficient to define an epileptic record; analysis of phase relations, waveform, location, responsiveness to stimuli, changes with time, and the effects of medication are necessary to provide diagnostic aid, let alone theoretical interest.

Lennox & Brody (200) noticed that out of 3,000 records, 211 showed "psychomotor" waves; of these only 135 had epilepsy, while 17 had proven, 14 probable subcortical lesions, and the remainder had a miscellany of conditions. The various EEG features grouped under the term "psychomotor" do not therefore seem to form a homogeneous diagnostic unit, but the one feature common to most of the cases is the disturbance of deeper structures and of their relation to cortex; in these conditions rhythmic discharges of the "theta" type (4 to 7 cycles per sec.) are common, and when these are combined with a slower component, the triangular, saw-tooth, flat topped, monophasic, or other psychomotor forms according to amplitude and phase relations inevitably appear. It has been demonstrated (109) that analysis of epileptic records often reveals many quasiharmonic components, even when the record shows relatively little abnormal activity, and some of these can usually be located to separate cortical regions. The inference that a seizure is due to exact synchronisation of these various rhythms is supported by the observation that in many such cases photic and other stimulation at the correct frequency does in fact evoke a typical attack (2, 74, 105, 109). The "alpha variants" described by Goodwin (218) and Proctor (148) have the same explanation, the alpha component in these cases being relatively large. Even in cases without seizures, the symptoms (emotional, vasomotor, or neurotic disturbances) are often relieved by "anticonvulsant" therapy, e.g., with hydantoinate (148, 149). The distinction or gradation between conditions characterised by overt seizures and those with psychic symptoms may only be a matter of measurement; in the epileptic there seem to be so many cortical and corticobasal mechanisms only just out of step that occasional synchrony and loss of function is inevitable—in the psychopath, only a few such exist, so that a general failure is unlikely, though restricted disturbances are common. Even in the normal, several rhythms occasionally "pull in" especially with the help of light anaesthesia and rhythmic stimulation, and in these conditions

irrational ideas, hallucinations, and impulsive acts can be induced.

The experimental study of epilepsy has been surveyed by Moruzzi (227) and Dawson's carefully controlled study of the relation between the EEG and muscle action potentials in myoclonic seizures (228) has been followed by his investigations of a case in which myoclonic jerkings could be induced by sensory stimulation (229). As compared with normals, the cortical potentials evoked by stimulation of a sensory nerve in this case were between five and ten times larger, and the response to the second of two stimuli was diminished when the interval between stimuli was 30 msecs., augmented at 60 to 100 msecs., again depressed at 140 msecs., and normal at 300 to 350 msecs. It is suggested that these differences from the normal response are due to an anomaly at the thalamic level and the similarity between the duration of the depression-recovery cycle and the usual wave-and-spike period is pointed out.

Walter & Walter (107) have studied similar cases in which jerkings followed rhythmic stimulation. In one, closing the eyes produced a large rhythm at 5 cycles per sec. from the parieto-occipital regions. When a flashing light was shone into the closed eyes, the 5 cycles per sec. rhythm was augmented and after a few seconds large spikes at the same frequency appeared in the frontal regions, synchronised with violent muscular jerks. All these effects ceased immediately on opening the eyes or when the flash frequency was changed, but similar responses were obtained with flashes at 7.5, 10, 12.5 and other multiples of 2.5 cycles per sec.; at the higher stimulus frequencies the responses were grouped, the group-frequency being 5 per sec., the interval between the two or three responses in the group that of the stimulus. The effects of several drugs were studied and the time relations of the components of the response measured. When the photic stimulation was prolonged, a major convulsion ensued. During recovery from this, photic stimulation was continued; the muscular jerkings were absent, while the cortical spikes persisted; contrariwise, after an apparently similar convulsion induced by electrical stimulation of the cortex, the cortical spikes were absent, but the muscular jerks remained.

The correspondence between these studies of "Divine preparations" and the animal experiments of Droogleever-Fortuyn & Jasper (2, 84, 85, 230) is close enough to foster hope that the functional pathology of epilepsy may soon be revealed.

The experimental approach is reflected in clinical applications by the increasing interest in "activated" electroencephalography. The use of small doses of convulsant drugs suggested by Ziskind, Sjaardema & Bercel (231) has been developed by Kaufman, Marshall & Walker (232) and Cure, Rasmussen & Jasper (233), who tried also the effects of hyperpnoea, hydration, electric shock, alcohol, trimethadione, penicillin, acetylcholine, and sodium cyanide. Intravenous metrazol was found the most satisfactory, giving activation in 44 per cent of ninety-seven patients at the first trial. Clinical seizures, resembling the spontaneous ones typical for the patient, occurred in 14 per cent but could be prevented by anticonvulsants. As well as diffuse effects, focal waves, spikes, and seizure patterns were evoked. The water-pitressin test has been studied by Blier & Redlich (234). The effects seem less specific than with metrazol but are considered of definite value in distinguishing epilepsy from other conditions. Wikler (235) gave the test to fourteen nonepileptics with previous drug addiction. In half of the records there was increased slow activity but there was no correlation with the degree of hydration. Cohn, Kolb & Mulder (236) found slow activity as often in nonepileptics as in epileptics and consider the test nonspecific and dangerous. Baïsset and others (237) found hypoglycaemia induced by intravenous insulin of value as an activator, and Bugnard and others (238) found lobeline effective in half of their cases. Palmer (239) claims that inhalations of ether to the point of tipsiness and also muscular effort, particularly swallowing, activate both diffuse and focal abnormalities. Gibbs & Gibbs (43, 44) encourage somnolence or sleep, finding that the proportion of abnormalities is more than doubled, whether the sleep is natural or assisted by soporifics.

When the cortex is exposed at operation, local electrical activation by minimal stimuli can be used to reveal epileptogenous zones (240).

Marsan & Fuortes (241) consider that the convulsions which sometimes follow intravenous injection of acetylcholine in man may be due to the reduction of cerebral blood flow, but Davis & Rémond (242) found that the local cortical oxygen tension is reduced not before but during and after seizure discharges due to metrazol. Gellhorn & Heymans (243) observed that anoxia depresses strychnine seizure patterns before it affects normal spontaneous activity. If hypoxia is both sufficient cause and inevitable

result of epileptic activity, it seems that all fits should be fatal; perhaps this tangle could be loosened by the judicious use of Occam's razor.

That activation should be produced by conditions as different as sleep and stimulation seems paradoxical. Perhaps it is only necessary to encourage electrical activity at about the right frequency in the right place. Whether the rhythm is a resting "spontaneous" one or an evoked one is not important; if it reaches a certain amplitude, there is a good chance that it will grow into a recognisable epileptic pattern—in an epileptic.

Psychiatric disturbances.—The EEG is not generally regarded as a diagnostic aid in mental disorders; it is the psychopaths and behaviour disorders whose resting records show the clearest abnormalities, generally of the theta type (149, 156, 157, 244 to 249). Eickhoff & Beevers (158) found no significant difference between normal and maladjusted children. In conditions of tension, normal or not, activity at 14 to 30 cycles per sec. is common (174, 250). As in all conditions, age and maturation are important factors (2). An abnormal EEG does not contraindicate electric shock therapy (249) which is agreed to produce reversible changes similar to those found after concussion (251 to 256) provided the treatment is not carried on too long. The first few treatments have the greatest effect upon the EEG and upon the excretion of 17-ketosteroids (257) .The effect of leucotomy is variable and correlates little with the clinical results (2, 258, 259).

As in other fields, the application of peripheral stimuli, activation by biochemical means, in general active, dynamic procedures involving stress and change, promise to reveal more than did the passive methods. Interesting anomalies appear from frequency and spatial analyses of the responses to photic stimulation (107) which in schizoid conditions are distributed differently from those of normals, and vary to some extent with slow changes in mental state. In some psychopathic personalities the evoked potentials are more of the juvenile type and fluctuate with mood and temper.

Miscellaneous.—Space restrictions prevent more than cursory reference to reports on isolated interesting cases; schistosomiasis (260), anencephaly (261), visceral inversion, osteopsathyrosis, facial hemihypertrophy (262, 263, 264). Dow & Whitty (265) reported on fifty-one cases of migraine—thirty presented abnormal EEGs at some phase of the migraine cycle, but no transient focal abnormalities were seen. Pacella and others (266) took records from guinea pigs, monkeys, and humans with poliomyelitis; acute infec-

tion in monkeys increased slow and fast activity as compared with alpha components, but only two convalescent cases out of seventeen humans, both with signs of encephalitis, showed any abnormalities. Hill (207) found flat records in five out of six cases of Huntington's chorea.

Unavoidably biassed, compressed, and abbreviated, this survey should nevertheless reflect a widening prospect of more fertile fields.

LITERATURE CITED

1. Walter, W. Grey, and Walter, V. J., EEG Bibliography (1946–1948); *EEG Society* (Burden Neurological Institute, Bristol, England)
2. Proc. 1st Internat. EEG Meeting, London, 1947, *Brit. Med. Bull.* (In press)
3. *Repts. Special Comm.*, Am. EEG Soc. (*Revised March, 1948*) (Mass. General Hospital, Boston)
4. *EEG Soc. Publications*, Recommendations for the Setting up of EEG Centres (1946)
5. Lennox, M. A., and Lennox, W. G., *Ann. Rev. Physiol.*, **9**, 507–24 (1947)
6. Bremer, F., *Ann. Rev. Physiol.*, **9**, 457–76 (1947)
7. Grundfest, H., *Ann. Rev. Physiol.*, **9**, 477–506 (1947)
8. Woolsey, C. N., *Ann. Rev. Physiol.*, **9**, 525–52 (1947)
9. McCulloch, W. S., and Lettvin, J. Y., *Ann. Rev. Physiol.*, **10**, 117–32 (1948)
10. Eccles, J. C., *Ann. Rev. Physiol.*, **10**, 93–116 (1948)
11. Lloyd, D. P. C., *Ann. Rev. Physiol.* (In press)
12. Magoun, H. W., *Ann. Rev. Physiol.* (In press)
13. Bremer, F., *J. belge neurol. psychiat.*, **47**, 9–28 (1947)
14. Gibbs, F. A., *Am. J. Psychiat.*, **102**, 527–35 (1946)
15. Gibbs, F. A., *Am. J. Psychiat.*, **103**, 519–22 (1947)
16. Jasper, H. H., *Epilepsy*, 181–203 (Grune & Stratton, New York, 1947)
17. Jasper, H. H., and Kershman, J., *Progress in Neurology and Psychiatry*, 372–97 (Grune & Stratton, New York, 1946)
18. van der Horst, L., *Psychiat. en Neurol. Bladen.*, 1–28 (1947)
19. Liberson, W. T., *Am. J. Psychiat.*, **104**, 456–60 (1948)
20. Tavares Bastos, A., *Cultura Méd.*, **8**, 68–88 (1946)
21. Rémy, M., *Monatsschr. Psychiat. Neurol.*, **111**, 183–223 (1945–46)
22. Rémy, M., *J. suisse med.*, **52**, 1363–73 (1947)
23. Barnes, T. C., *Confinia Neurol.*, **8**, 73–125 (1947)
24. Baudouin, A., *Semaine hôp. (Paris)*, **22**, 1209–17 (1946)
25. Delay, J., and Verdeaux, G., and Verdeaux, J., *Encephale* (3), **79–96** (1946–47)
26. Frey, T. S., *Acta Psychiat. et Neurol.*, Suppl. 42, 1–172 (1946)
27. Kornmüller, A. E., *Arch. Psychiat. Nervenkrankh.*, **116**, 608–47 (1943)
28. Kornmüller, A. E. (Georg Thieme, Stuttgart, 1947)
29. Walter, W. Grey, *Nevropatol. i Psikhiatr.*, **15**, 43–52 (1946)
30. Cobb, S., *Arch. Neurol. Psychiat.*, **59**, 63–98 (1948)
31. Hill, D., Walter, W. Grey, Cobb, W. A., Whitteridge, D., Greville, G. D., Heppenstall, M., and Parr, G., *Electro-encephalography* (Macdonald, London, In press)

32. JOHNSTON, D. L., *Wireless Eng.*, **24**, 231–42 (Aug., 1947)
33. JOHNSTON, D. L., *Wireless Eng.*, **24**, 271–77 (Sept., 1947)
34. JOHNSTON, D. L., *Wireless Eng.*, **24**, 292–97 (Oct., 1947)
35. WALTER, W. GREY, AND BROOKS, A. A., *Electronic Eng.*, **19**, 221–26 (1947)
36. MATTHEWS, B. H. C., *J. Sci. Instruments* (In press)
37. CONRAD, M., AND PACELLA, B. L., *Science*, **105**, 216 (1947)
38. BENDHEIM, O. L., *J. Am. Med. Assoc.*, **131**, 645 (1946)
39. BAGCHI, B. K., AND BASSETT, R. C., *J. Neurosurg.*, **4**, 348–69 (1947)
40. COHN, R., *J. Neurophysiol.*, **11**, 31–37 (1948)
41. BARNES, T. C., AND AMOROSO, M. D., *Federation Proc.*, **6**, 74 (1947)
42. LAPLANE, R., FISCHGOLD, H., AND BRISAC, C., *Nourrisson*, **35**, 59–63 (1947)
43. GIBBS, E. L., AND GIBBS, F. A., *Research Pubs., Assoc. Research Nervous Mental Disease*, **26** (In press)
44. Abstracts Am. EEG Soc., 2nd Ann. Meet., 6 pp. (Atlantic City, June 12–14, 1948)
45. BUFFINGTON, M. A., AND WEIL, A. A., *Science*, **105**, 185–86 (1947)
46. DARROW, C. W., AND PATHMAN, J. H., *Science*, **103**, 22 (1946)
47. MCINTYRE, A. R., AND DUNN, A. L., *Arch. Neurol. Psychiat.*, **56**, 686–90 (1946)
48. NIXON, D. L., *Arch. Neurol. Psychiat.*, **56**, 691–93 (1946)
49. WALTER, W. GREY, AND DOVEY, V. J., *Lancet*, **I**, 5–9 (1946)
50. LENNOX, M., AND RUCH, T. C., *J. Neurosurg.*, **3**, 219–22 (1946)
51. ROUBICEK, J., AND HILL, D., *Brain*, **71**, 77–87 (1948)
52. GASTAUT, H., *Présentation d'une Electrode Pharyngée Bipolaire* (Presented at 1st Meeting French EEG Soc., Paris, March 5, 1948); *Digest Neurol. Psychiat. Inst. of Living*, 385 (June, 1948)
53. JASPER, H. H., FAURE, J., AND HENDERSON, L., *J. Electroenceph. Clin. Neurophysiol.* (In press)
54. RÉMOND, A., *Les Electrodes dites "Tripodes" et leur dispositif de fixation* (Presented at 1st Meeting French EEG Soc., Paris, March 5, 1948)
55. ENGEL, G. L., AND HOAGLAND, H., *Arch. Neurol. Psychiat.*, **57**, 379–83 (1947)
56. BALDOCK, G. R., AND WALTER, W. GREY, *Electronic Eng.*, **18**, 339–44 (1946)
57. BARBOUR, I., *Rev. Sci. Instruments*, **18**, 516–22 (1947)
58. GIBBS, F. A., AND GRASS, A. M., *Science*, **105**, 132–34 (1947)
59. BUGNARD, L., *Semaine hôp. (Paris)*, **22**, 1247–50 (1946)
60. WALTER, W. GREY, *J. Nervous Mental Disease*, **107**, 82–84 (1948)
61. SONNEMANN, H., AND KENNARD, M. A., *Science*, **105**, 437–38 (1947)
62. GUALTIEROTTI, T., *Arch. psicol. neurol. psichiat.*, **6**[3], 1–11 (July, 1945)
63. GUALTIEROTTI, T., *Schweiz. Arch. Neurol. Psychiat.*, **59**, 145–51 (1947)
64. BERTRAND, I., AND LACAPE, R. S., *Théorie de L'Electro-encephalogramme*, 1–156 (Gaston Doin & Co., Paris, France, 1943)
65. BOYD, W. E., *J. Brit. Inst. Radio Engrs.*, 1–13 (Mar.–April, 1948)
66. RÉMY, M., *Monatsschr. Psychiat. Neurol.*, **115**, 161–80 (1948)
67. MARK, D. D., *Am. J. Physiol.*, **149**, 538–48 (1947)
68. THIESEN, J. W., *J. Nervous Mental Disease*, **106**, 447–63 (1947)
69. DARROW, C. W., *Am. J. Psychiat.*, **102**, 791–98 (1946)
70. DARROW, C. W., AND HENRY, C. E., *Am. Psychologist*, **10**, 421 (1947)
71. DARROW, C. W., PATHMAN, J. H., AND KRONENBERG, G., *J. Exptl. Psychol.*, **36**, 355–65 (1946)

72. HILL, D., ST. JOHN-LOE, P., THEOBALD, J., AND WADDELL, M., *Brain* (In press)
73. DAWSON, G. D., *J. Neurol. Neurosurg. Psychiat.*, **10**, 137–40 (1947)
74. WALTER, W. GREY, DOVEY, V. J., AND SHIPTON, H. W., *Nature*, **158**, 540–41 (1946)
75. ADRIAN, E. D., *The Physical Background of Perception*, 95 pp. (Oxford University, 1947)
76. MCCULLOCH, W. S., *Federation Proc.*, **6**, 448–51 (1947)
77. PITTS, W., AND MCCULLOCH, W. S., *Bull. Math. Biophys.*, **9**, 127–47 (1947)
78. DARROW, C. W., *Psychol. Rev.*, **54**, 157–68 (1947)
79. ASHBY, W. R., *J. Mental Sci.*, **92**, 319–23 (1946)
80. ASHBY, W. R., *J. Gen. Psychol.*, **37**, 125–28 (1947)
81. ASHBY, W. R., *Psychometrika.*, **12**, 135–40 (1947)
82. ASHBY, W. R., *J. Comp. Physiol. Psychol.*, **40**, 1–7 (1947)
83. ROSENBLUETH, A., WIENER, N., AND BIGELOW, J., *Philosophy Sci.*, **10**, 18–24 (1943)
84. DROOGLEEVER-FORTUYN, J., AND JASPER, H. H., *Proc. 17th Intern. Physiol. Congr. Oxford*, 368–69 (1947)
85. DROOGLEEVER-FORTUYN, J., AND JASPER, H. H., *J. Neurophysiol.* (Unpublished data)
86. MARGARIA, R., *Arch. neerland physiol.*, **28**, 399–407 (1946)
87. GUALTIEROTTI, T., MARTINI, E., AND MARZORATI, A., *Boll. soc. ital. biol. sper.*, **21**, 55–57 (1946)
88. GUALTIEROTTI, T., MARTINI, E., AND MARZORATI, A., *Boll. soc. ital. biol. sper.*, **21**, 50–55 (1946)
89. SPERRY, R. W., *J. Neurophysiol.*, **10**, 275–94 (1947)
90. LEÃO, A. A. P., *J. Neurophysiol.*, **10**, 409–14 (1947)
91. GEREBTZOFF, M. A., *Arch. intern. physiol.*, **51**, 365–78 (1941)
92. WARD, A. A., PEDEN, J. K., AND SUGAR, O., *J. Neurophysiol.*, **9**, 453–61 (1946)
93. GELLHORN, E., AND BALLIN, H. M., *Am. J. Physiol.*, **146**, 630–35 (1946)
94. GELLHORN, E., *J. Neurophysiol.*, **10**, 125–32 (1947)
95. BARKER, S. H., AND GELLHORN, E., *J. Neurophysiol.*, **10**, 133–38 (1947)
96. FORSTER, F. M., BORKOWSKI, W. J., AND MCCARTER, R. H., *J. Neuropathol. Exptl. Neurol.*, **5**, 364–73 (1946)
97. GREENBLATT, M., FUNKENSTEIN, O., MILLER, D., AND RINKEL, M., *Am. J. Psychiat.*, **103**, 749–57 (1947)
98. WARD, A. A., JR., AND MCCULLOCH, W. S., *J. Neurophysiol.*, **10**, 309–14, (1947)
99. WARD, A. A., JR., *J. Neurophysiol.*, **11**, 13–23 (1948)
100. MCCULLOCH, W. S., GRAF, C., AND MAGOUN, H. W., *J. Neurophysiol.*, **9**, 127–32 (1946)
101. FRENCH, J. D., SUGAR, O., AND CHUSID, J. G., *J. Neurophysiol.*, **11**, 185–92 (1948)
102. SUGAR, O., FRENCH, J. D., AND CHUSID, J. G., *J. Neurophysiol.*, **11**, 175–84 (1948)
103. BOSMA, J. F., AND GELLHORN, E., *J. Neurophysiol.*, **9**, 263–74 (1946)
104. DELGADO, J. M. R., FULTON, J. F., AND LIVINGSTON, R. B., *Federation Proc.*, **6**, 95–96 (1947)

105. WALTER, W. GREY, WALTER, V. J., GASTAUT, H., AND GASTAUT, Y., *Une forme élétroencephalogrpahie nouvelle de l'épilepsie, l'épilepsie photogenique* (Presented at 1st Meeting French EEG Soc., Paris, March 5, 1948)
106. BERTRAND, I., GODET-GUILLAIN, J., AND MAZARS, G., *Compt. rend soc. biol.*, **139,** 29–30 (1945)
107. WALTER, W. GREY, AND WALTER, V. J., *J. Elector-enceph. Clin. Neurophysiol.* (In press)
108. LIVANOV, M. N., AND POLIAKOV, K. L., *Bull. acad. sci. U.R.S.S.*, No. 3, 286–307 (1945)
109. WALTER, W. GREY, *Research Pubs., Assoc. Research Nervous Mental Disease,* **26,** 237–51 (1946)
110. MONNIER, M., *J. Electroenceph. Clin. Neurophysiol.* (In press)
111. GASTAUT, H. (Personal communication, 1948)
112. DELGADO, J. M. R., AND LIVINGSTON, R. B., *J. Neurophysiol.*, **11,** 39–55 (1948)
113. FAIRWEATHER, D. S., O'SULLIVAN, H. J. L., AND WALTER, W. GREY, *Unverricht's Myoclonic Epilepsy in Identical Twins* (Presented EEG Soc. Meeting, Bristol, England, May 1, 1948)
114. ENGEL, G. L., WEBB, J. P., AND FERRIS, E. B., *J. Clin. Invest.*, **24,** 691–97 (1945)
115. FINESINGER, J. E., LINDEMANN, E., BRAZIER, M. A. B., AND CHAPPLE, E. D., *Am. J. Psychiat.*, **103,** 738–48 (1947)
116. GELLHORN, E., AND BALLIN, H. M., *Am. J. Physiol.*, **146,** 559–66 (1946)
117. SWINYARD, E. A., TOMAN, J. E. P., AND GOODMAN, L. S., *J. Neurophysiol.*, **9,** 47–54 (1946)
118. GRENELL, R. G., AND MCCAWLEY, E. L., *J. Neurosurg.*, **4,** 508–18 (1947)
119. VAN HARREVELD, A., *J. Neurophysiol.*, **10,** 361–70 (1947)
120. BRAZIER, M. A. B., *J. Neurol. Neurosurg. Psychiat.*, **11,** 118–33 (1948)
121. ECCLES, J. C., *J. Neurophysiol.*, **10,** 197–204 (1947)
122. BULLOCK, T. H., GRUNDFEST, H., NACHMANSOHN, D., AND ROTHENBERG, M. A., *J. Neurophysiol.*, **10,** 11–22 (1947)
123. WHITTERIDGE, D., *J. Neurol. Neurosurg. Psychiat.*, **11,** 134–40 (1948)
124. BORNSTEIN, M. B., *J. Neurophysiol.*, **9,** 349–66 (1946)
125. BARNES, T. C., *Proc. 17th Intern. Physiol. Congr. Oxford*, 60–61 (1947)
126. BARNES, T. C., *Biol. Bull.*, **93,** 222 (1947)
127. BARNES, T. C., AND MAUER, I., *Arch. intern. pharmacodynamie,* **73,** 386–91 (1947)
128. JOHNSON, H. C., WALKER, A. E., CASE, T. J., AND KOLLROS, J. J., *Arch. Neurol. Psychiat.*, **56,** 184–97 (1946)
129. WALKER, A. E., AND JOHNSON, H. C., *Penicillin in Neurology*, 47–101 (Charles C Thomas, Springfield, Illinois)
130. SUCKLE, H. M., LIEBENOW, R. R., AND ORTH, O. S., *J. Neurosurg.*, **4,** 370–79 (1947)
131. BORKOWSKI, W. J., AND FORSTER, F. M., *J. Neuropathol. Exptl. Neurol.*, **6,** 201–5 (1947)
132. ENGEL, G. L., ROMANO, J., AND FERRIS, E. B., *Arch. Neurol. Psychiat.*, **58,** 337–50 (1947)
133. CRESCITELLI, F., AND GILMAN, A., *Am. J. Physiol.*, **147,** 127–37 (1946)
134. HAYMAKER, W., GINZLER, A. M., AND FERGUSON, R. L., *Am. J. Med. Sci.*, **212,** 423–31 (1946)

135. ENGEL, G. L., ROMANO, J., AND GOLDMAN, L., *Arch. Neurol. Psychiat.*, **56**, 659–64 (1946)
136. NEWELL, G. W., ERICKSON, T. C., GILSON, W. E., AND ELVEHJEM, C. A., *Proc. Soc. Exptl. Biol. Med.*, **65**, 115–16 (1947)
137. SILVER, M. L., JOHNSON, R. E., KARK, R. M., KLEIN, J. R., MONAHAN, E. P., AND ZEVIN, S. S., *J. Am. Med. Assoc.*, **135**, 757–60 (1947)
138. WARD, A. A., JR., *J. Neurophysiol.*, **10**, 105–11 (1947)
139. TOMAN, J. E. P., SWINYARD, E. A., AND GOODMAN, L. S., *J. Neurophysiol.*, **9**, 231–40 (1946)
140. TOMAN, J. E. P., LOEWE, S., AND GOODMAN, L. S., *Arch. Neurol. Psychiat.*, **58**, 312–24 (1947)
141. PERLSTEIN, M. A., *Arch. Neurol. Psychiat.*, **55**, 164–65 (1946)
142. PERLSTEIN, M. A., AND ANDELMAN, M. B., *J. Pediat.*, **29**, 20–40 (1946)
143. PERLSTEIN, M. A., *Am. J. Psychiat.*, **104**, 247–53 (1947)
144. GIBBS, F. A., *Ann. Internal Med.*, **27**, 548 (1947)
145. LENNOX, W. G., *Am. J. Psychiat.*, **103**, 159–61 (1946)
146. LENNOX, W. G., *J. Pediat.*, **29**, 356–62 (1946)
147. LENNOX, W. G., *Am. J. Psychiat.*, **103**, 457–62 (1947)
148. PROCTOR, L. D., *Am. J. Psychiat.*, **104**, 380–86 (1947)
149. WALKER, C. F., AND KIRKPATRICK, B. B., *Am. J. Psychiat.*, **103**, 484–92 (1947)
150. BARNES, T. C., *Federation Proc.*, **6**, 74 (1947)
151. GIRDEN, E., *J. Neurophysiol.*, **11**, 169–74 (1948)
152. MCINTYRE, A. R., DUNN, A. L., AND FULLER, P. E., *Federation Proc.*, **5**, 67 (1946)
153. EVERETT, G. M., *Federation Proc.*, **6**, 101 (1947)
154. TYLER, D. B., *Am. J. Physiol.*, **150**, 253–62 (1947)
155. WATSON, C. W., *Yale J. Biol. Med.*, **19**, 127–35 (1946)
156. GOTTLIEB, J. S., ASHBY, M. C., AND KNOTT, J. R., *Arch. Neurol. Psychiat.*, **56**, 381–400 (1946)
157. GOTTLIEB, J. S., ASHBY, M. C., AND KNOTT, J. R., *Am. J. Psychiat.*, **103**, 823–27 (1947)
158. EICKHOFF, L. F. W., AND BEEVERS, C. A., *Am. J. Psychiat.*, **104**, 194–96 (1947)
159. GIBBS, F. A., AND KNOTT, J., *J. Electroenceph. Clin. Neuro-physiol.* (In press)
160. TURNER, O. A., *Arch. Neurol. Psychiat.*, **59**, 1–12 (1948)
161. PENTZIK, A. S., *Works Brain Inst. Moscow.*, **5**, 273–85 (1940)
162. HILL, D., in Garrod, Thursfield & Batten's *Textbook of Children's Diseases* (In press)
163. ROBINSON, L. J., AND OSTERHELD, R. G., *J. Nervous Mental Disease*, **106**, 464–70 (1947)
164. BARNES, T. C., AND FISCHER, C. C., *Arch. Pediat.*, **64**, 6–24 (1947)
165. MELIN, K. A., *Svenska Läkartidn.*, **43**, 2601–7 (1946)
166. ROBINSON, L. J., *J. Nervous Mental Disease*, **104**, 486–88 (1946)
167. ENGEL, G. L., ROMANO, J., AND FERRIS, E. B., *Science*, **105**, 600–1 (1947)
168. BJERNER, B., AND STEINWALL, O., *Nord. Med.*, **34**, 967–72 (1947)
169. DIAZ-GUERRERO, R., GOTTLIEB, J. S., AND KNOTT, J. R., *Psychosomat. Med.*, **8**, 399–404 (1946)
170. TYLER, D. B., GOODMAN, J., AND ROTHMAN, T., *Am. J. Physiol.*, **149**, 185–93 (1947)
171. BARNES, T. C., AND AMOROSO, M. D., *Federation Proc.*, **6**, 75 (1947)
172. DYNES, J. B., *Arch. Neurol. Psychiat.*, **57**, 84–93 (1947)

173. Fischgold, H., and Bounes, G. C., *Semaine hôp. (Paris)*, **22,** 1245–47 (1946)
174. Cohn, R., *J. Nervous Mental Disease*, **104,** 351–57 (1946)
175. Adrian, E. D., *Practitioner*, **158,** 76–82 (1947)
176. Weddell, G., Sinclair, D. C., and Feindel, W. H., *J. Neurophysiol.*, **11,** 99–109 (1948)
177. Spiegel, E. A., Henny, G. C., Wycis, H. T., and Spiegel-Adolf, M., *Am. J. Physiol.*, **146,** 12–21 (1946)
178. Zimmerman, F. T., and Putnam, T. J., *Arch. Neurol. Psychiat.*, **57,** 521–46 (1947)
179. Ward, J. W., and Clark, S. L., *J. Neurophysiol.*, **11,** 59–74 (1948)
180. Blinkov, S. M., Livanov, M. N., and Rosinov, V. S., *Voprosy Nevrokhirurg.*, **9,** 49–54 (1945)
181. Cramer, F., Pastor, S., and Stephenson, C. (Discussed by Storch, T. J. C.) *J. Nervous Mental Disease*, **106,** 602–5 (1947)
182. Laufer, M. W., and Perkins, R. F., *J. Nervous Mental Disease*, **104,** 583–92 (1946)
183. Laufer, M. W., and Perkins, R. F., *J. Nervous Mental Disease*, **106,** 619–30 (1947)
184. Roseman, E., and Woodhall, B., *Research Pubs., Assoc. Research Nervous Mental Disease*, **25,** 200–19 (1946)
185. Puech, P., Fischgold, H., Verdeaux, G., and Verdeaux, J., *Semaine hôp. (Paris)*, **22,** 1233–42 (1946)
186. Roseman, E., *J. Nervous Mental Disease*, **105,** 319–21 (1947)
187. Kaufman, I. C., and Walker, A. E., *J. Nervous Mental Disease* (In press)
188. Murphy, J. P., and Garvin, J. S., *Arch. Neurol. Psychiat.*, **58,** 436–46 (1947)
189. Bassett, R. C., and Bagchi, B. K., *Univ. Hosp. Bull., Ann Arbor*, **13,** 11–12 (1947)
190. Baudouin, A., Puech, P., Fischgold, H., and Lerique-Koechlin, A., *Semaine hôp. (Paris)*, **22,** 1226–33 (1946)
191. Buchthal, F., and Busch, E., *Acta Psychiat. et Neurol.*, **22,** 9–17 (1947)
192. Hill, D., *Marseille méd.*, **84** (5), 215–231 (1947)
193. Hoefer, P. F. A., Schlesinger, E. B., and Pennes, H. H., *Arch. Neurol. Psychiat.*, **58,** 118–20 (1947)
194. Høncke, P., and Malmros, R., *Nord. Med.*, **35,** 1762 (1947)
195. Mosovich, A., *Anales VII congr. nacl. med. (La Plata)* (In press)
196. Pupo, P. P., and Pimenta, A. M., *Arq. neuro-psiquiat. (São Paulo)*, **4,** 373–90 (1946)
197. Sager, O., and Kreindler, A., *Presse méd.*, **55,** 195–96 (1947)
198. Schlesinger, B., and Strauss, H., *J. Mt. Sinai Hosp., N. Y.*, **14,** 47–50 (1947)
199. Viale, S. M., and Odoriz, J. B., *Arch. Neurocir. (Buenos Aires)*, **1,** 299–314 (1944)
200. Lennox, M., and Brody, B., *J. Nervous Mental Disease*, **104,** 237–48 (1946)
201. Laufer, M. W., *J. Nervous Mental Disease*, **106,** 527–36 (1947)
202. Puech, P., Fischgold, H., Brisac, C., and Morice, J., *Monde méd. (Paris)*, No. 12, 121–25 (1947)
203. Gibbs, F. A., and Gibbs, E. L., *Arch. Neurol. Psychiat.*, **58,** 184–92 (1947)
204. Hoefer, P. F. A., Schlesinger, E. B., and Pennes, H. H., *Research Pubs., Assoc. Research Nervous Mental Disease*, **26** (In press)
205. Paillas, J. E., Gastaut, H., Tamalet, J., and Verspyck, H., *Rev. neurol.* (In press)

206. STUHL, L., FISCHGOLD, H., AND DELL, M., *J. Radiolog. et d'Electrologie*, **28**, 239–41 (1947)
207. WALTER, W. GREY, HILL, D., AND WILLIAMS, D., *Proc. Roy. Soc. Med.*, **41**, 237–50 (1948)
208. WOOLF, J. I., WALKER, A. E., KNOX, G. W., AND HALSTEAD, W. C., *J. Neuropathol. Exptl. Neurol.*, **4**, 59–67 (1945)
209. ABBOTT, J. A., *J. Nervous Mental Disease*, **105**, 535–40 (1947)
210. BAUDOUIN, A., FISCHGOLD, H., AND RÉMOND, A., *Semaine hôp. (Paris)*, **22**, 1217–21 (1946)
211. BAUDOUIN, A., FISCHGOLD, H., DELARUE, R., AND CLOCHE, R., *Semaine hôp. (Paris)*, **22**, 1221–24 (1946)
212. CLOCHE, R., *L'électro-encephalographie dans l'épilepsie* (Librairie le Francois, 1–147, 1945)
213. DICK, T. S. B., *Lancet*, **I**, 555–57(1947)
214. HØNCKE, P., *Nord. Med.*, **29**, 549–54 (1946)
215. PARFITT, N. D., *Lancet*, **I**, 483 (1947)
216. SUBIRANA, A., *Medicamenta (Madrid)*, **6** (144), 158–64 (1948)
217. SUBIRANA, A., AND OLLER-DAURELLA, L., *Med. clin. (Barcelona)*, **8**, 151–63 (1947)
218. GOODWIN, J. E., *Am. J. Psychiat.*, **104**, 369–79 (1947)
219. HOEFER, P. F. A., GUTTMAN, S. A., AND SANDS, I. J., *Am. J. Psychiat.*, **102**, 486–95 (1946)
220. KENNARD, M. A., AND WILLNER, M. D., *Research Pubs., Assoc. Research Nervous Mental Disease* (In press)
221. LAPLANE, R., FISCHGOLD, H., BRISAC, C., AND FRITAL, D., *Nourrisson*, **35**, 64–76 (1947)
222. ESCARDO, F., AND MOSOVICH, A., *Aspectos electro-encefalograficos de la Epilepsia Infantil*, 1–65 (El Ateneo, Buenos Aires, 1948)
223. WHITEACRE, W. M., LOEB, J. N., AND CHIN, H., *J. Am. Med. Assoc.*, **133**, 445–49 (1947)
224. DELAY, J., FISCHGOLD, H., PICHOT, P., AND VERDEAUX, G., *L'epilepsie myoclonique du type Unverricht Génétique, constatations élétro-encephalographiques, Soc. Neurol.*, June (1947)
225. DELAY, J., SUTTEL, R., AND VERDEAUX, G., *Semaine hôp. (Paris)*, **23**, 1874–77 (1947)
226. SHAW, D., AND HILL, D., *J. Neurol. Neurosurg. Psychiat.*, **10**, 107–17 (1947)
227. MORUZZI, G., *L'epilessia sperimentale*, **1**, 1–128 (1945)
228. DAWSON, G. D., *J. Neurol. Neurosurg. Psychiat.*, **9**, 5–22 (1946)
229. DAWSON, G. D., *J. Neurol. Neurosurg. Psychiat.*, **10**, 141–62 (1947)
230. JASPER, H. H., AND DROOGLEVER-FORTUYN, J. D., *Research Pubs., Assoc. Research Nervous Mental Disease* (In press)
231. ZISKIND, E., SJAARDEMA, H., AND BERCEL, N. A., *Science*, **104**, 462–63 (1946)
232. KAUFMAN, I. C., MARSHALL, C., AND WALKER, A. E., *Arch. Neurol. Psychiat.*, **58**, 533 (1947)
233. CURE, C., RASMUSSEN, T., AND JASPER, H. H., *Arch. Neurol. Psychiat.* (In press)
234. BLIER, J. S., AND REDLICH, F. C., *Arch. Neurol. Psychiat.*, **57**, 211–19 (1947)
235. WIKLER, A., *Arch. Neurol. Psychiat.*, **57**, 78–83 (1947)
236. COHN, R., KOLB, L. C., AND MULDER, D. W., *J. Nervous Mental Disease*, **106**, 513–26 (1947)
237. BAÏSSET, A., BUGNARD, L., GREZES-RUEFF, F. A., GREZES-RUEFF, C., AND

PLANQUES, J., *X Veme Reunion Assoc. Physiol. Langue Franc.* (April 17, 1947)

238. BUGNARD, L., PLANQUES, J., GREZES-RUEFF, F. A., AND GREZES-RUEFF, C., *Semaine hôp. (Paris)*, **22,** 1225–26 (1946)
239. PALMER, H. (Personal communication, 1948)
240. WALKER, A. E., QUADFASEL, F. A., MARSHALL, C., NETSKY, M. G., FISHER, R. G., KAUFMAN, I. C., GERHARDT, J. W., AND BERESFORD, E. N., *Arch. Neurol. Psychiat.*, **59,** 254–58 (1948)
241. MARSAN, C. A., AND FUORTES, M. G. F., *Riv. neurol.*, **18,** 1–10 (1948)
242. DAVIS, P. W., AND RÉMOND, A., *Proc. Assoc. Research Nervous Mental Disease*, **26,** 205–17 (1946)
243. GELLHORN, E., AND HEYMANS, C., *J. Neurophysiol.*, **11,** 261–73 (1948)
244. KIBBE, M. H., *New Engl. J. Med.*, **237,** 122–25 (1947)
245. MOSOVICH, A., "La electroencefalographia en Psiquiateria," in Dr. E. Mira y Lopez' *Psiquiateria*, 3rd Ed. (El Ateneo, Buenos Aires, 1946)
246. SIMONS, D. J., AND DIETHELM, O., *Arch. Neurol. Psychiat.*, **55,** 619–26 (1946)
247. ROCKWELL, F. V., AND SIMONS, D. J., *Arch. Neurol. Psychiat.*, **57,** 71–77 (1947)
248. SIMON, B., O'LEARY, J. L., AND RYAN, J. J., *Arch. Neurol. Psychiat.*, **56,** 677–85 (1946)
249. TAYLOR, R. M., AND PACELLA, B. L., *J. Nervous Mental Disease*, **107,** 220–27 (1948)
250. SHPILBERG, P. I., *Bull. biol. méd. exptl. U.R.S.S.*, **23,** 124–28 (1947)
251. CORNIL, L., GASTAUT, H., OLLIVIER, H., AND CAIN, J., *Semaine hôp. (Paris)*, **22,** 686–89 (1946)
252. CREMERIUS, J., AND JUNG, R., *Nervenarzt*, **18,** 193–205 (1947)
253. MORIARTY, J. D., AND SIEMENS, J. C., *Arch. Neurol. Psychiat.*, **57,** 712–18 (1947)
254. WEIL, A. A., AND BRINEGAR, W. C., *Arch. Neurol. Psychiat.*, **57,** 719–29 (1947)
255. GOTTLIEB, J. S., KNOTT, J. R., AND KIMBLE, L. L., *Am. J. Psychiat.* (In press)
256. RUBINSTEIN, H. S., AND KURLAND, A. A., *Proc. Soc. Exptl. Biol. Med.*, **65,** 348–51 (1947)
257. HOAGLAND, H., MALAMUD, W., KAUFMAN, I. C., AND PINCUS, G., *Psychosomat. Med.*, **8,** 246–51 (1946)
258. GREVILLE, G. D., AND LAST, S. L., *Proc. Roy. Soc. Med.*, **40,** 145–47 (1947)
259. STEVENS, H., AND MOSOVICH, A., *Am. J. Psychiat.*, **104,** 73–80 (1947)
260. WATSON, C. W., MURPHY, F., AND LITTLE, S. C., *Arch. Neurol. Psychiat.*, **57,** 199–210 (1947)
261. PUECH, P., GUILLY, P., FISCHGOLD, H., AND BRISAC, C., *Rev. neurol.*, **79,** 117 (1947)
262. CORNIL, L., SCHACHTER, M., AND GASTAUT, H., *Marseille méd.*, **83,** 538–42 (1946)
263. CORNIL, L., SCHACHTER, M., AND GASTAUT, H., *Rev. neurol.*, **78,** 380–82 (1946)
264. CORNIL, L., SCHACHTER, M., AND GASTAUT, H., *Rev. neurol.*, **78,** 260–61 (1946)
265. DOW, D. J., AND WHITTY, C. W. M., *Lancet*, **II,** 52–54 (1947)
266. PACELLA, B. L., JUNGEBLUTT, C. W., KOPELOFF, N., AND KOPELOFF, L. M., *Arch. Neurol. Psychiat.*, **58,** 447–51 (1947)

HEARING

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Introduction

This review of the research and studies of the function of hearing covers the period from 1945 to the present. During this time considerable additional factual information has been obtained on the basic physiological processes of hearing, the anatomical arrangements for pitch and intensity discrimination in the cochlea, and the transmission of response of sound to the higher brain centers.

Much of this work concerning the function of the higher auditory centers stems from researches of the period immediately preceding 1945 during which so much of our present knowledge of this subject was developed. Recent work must, therefore, be read with the previous researches constantly in mind.

The clinical aspects of otology have always been of great interest to those concerned with the theoretical aspects of the field, and, indeed, a great deal of our knowledge of the mechanisms of auditory function has had its origin in clinical material. For this reason some pertinent clinical papers are included in this discussion.

Cochlear Mechanics

A translation of earlier articles (1, 2) by von Békésy on the physical properties of the various membranes of the cochlea has been recently published in the *Journal of the Acoustical Society*. In these papers, the techniques developed by von Békésy for studying the elasticity of the cochlear partition between the scala tympani and scala vestibuli are described. One technique was to press on the basilar membrane with a minute rod and to observe the area of deformation. He found that near the apex the tension was almost the same longitudinally as vertically, while near the stapes the ratio of vertical to longitudinal tension was about two to one. However, he also concluded from observing minute cuts in the basilar membrane that this structure is under very little tension and resembles a gelatinous sheet covered by a thin layer of fibers. This

author attempted to measure the absolute elasticity of the cochlear partition by observing the deformation of the structure by change in pressure on the two siders. He also describes an acoustic method for measuring elasticity of the cochlear partition.

This author has also devised an ingenious optical means of measuring the phase relations of the sound within the cochlea. He concluded that sinusoidal vibration of the stapes sets up a traveling wave within the cochlear partition. He attempts to estimate the elastic properties of the various tissues within the cochlear duct and concludes that the only structure exhibiting any significant continuous change in elasticity is the basilar membrane. He claims that this supports Hensen & Helmholtz's thesis that the location of the maximum vibration for a particular tone is determined by this structure.

Since Galambos & Davis (3) have shown that the nerve impulses occur at a constant part of the sound cycle, it has seemed evident that a phase difference between oval and round windows must play a role in hearing. Von Békésy (4) has studied the sound pressure and phase differences between the two windows in human cadaver material by means of differential microphones. With the middle ear mechanism intact, he found twentyfold pressure transformation between the ear drum and the stapes. In temporal bones with the drum absent, the pressure difference is found to be too small to account for hearing ability of patients with similar pathology. He suggests this discrepancy may be due to the resonance of pneumatic cells of the mastoid process. The experience of surgeons who have obtained perfectly normal hearing in patients following fenestration operation for otosclerosis makes one feel that our knowledge is very incomplete as to the role of the middle ear mechanism in the passage of sound from the air to the inner ear fluids.

Pohlman (5) has made some interesting observations in patients whom he was fitting with an artificial middle ear. He found that placing the acoustic probe in contact with either the round or oval windows in some patients was effective in restoring hearing. However, the patients described a difference in the quality of the sound from the two windows. This observation would argue in favor of pressure differences between the two windows as the mechanism of stimulation.

Kobrak (6) has described a method of recording optically the

movements of the ossicles from the oval and round window membranes. This method should be useful in the study of the mechanics of the middle ear.

Several writers have attempted deductive analysis of the mechanism of hearing based on the accumulation of data from several sources. Licklider (7), in a study of the sharpness of tuning of different parts of the organ of Corti to various tones, has compared the evidence from a number of indirect methods with that from direct observations of the basilar membrane by von Békésy. He concludes that frequency selectivity increases with decrease in pitch down to one hundred cycles. He attempts to reconcile this with conflicting observations from psychophysical experiments that indicate no change below one thousand cycles.

Gabor (8) has undertaken a mathematical analysis of experiments on the duration required for a pure tone to be heard as such. He considers the possibility of two mechanisms in the cochlea for the appreciation of sounds of short and long duration. He suggests that if a pure tone is continued, there is gradual inhibition of adjacent nerve fibers and consequent production of much sharper pitch discrimination than one would expect from the broad tuning of mechanical resonators suggested by many experiments.

Tumarkin (9) has analyzed the data relating to the paradoxical properties of the cochlea of critical damping and high selectivity. He concludes that the ear is heavily damped but not critically damped. He considers this damping to be the result of the radiating of energy back into the air as a result of the elasticity of the middle and inner ear mechanisms. He postulates a fall of pressure to zero at the spot on the basilar membrane optimum for a particular tone as explanation for the fact that low tones mask high tones but not vice versa.

The full length paper on the development of the organ of Corti of the opossum by Larsell, McCrady & Larsell (10) has appeared. This extremely careful correlation of histological structure of the organ of Corti with the functional ability as shown by cochlear potentials gives some indication of the significance of the supporting structures of the organ of Corti. These authors find the earliest differentiation of the organ of Corti to the functional stage to occur in the upper basal and lower medial coils. They consider the important points of differentiation to be the formation of the pillars of Corti, the tunnel, the phalangeal cells, the reticular plate, and

the hair cells. The earliest tones to which response was obtained were one thousand to thirteen hundred cycles per second. With the extension of the area of completely developed organ of Corti, there was increase in the range of tones causing response until the whole frequency range from two hundred to twenty-six thousand cycles per second was reached. There was some evidence of migration of the loci for low tones as the differentiation progressed. The investigations of these authors showed that the sensitivity of the organ of Corti increased greatly with the development of the tunnel and other supporting apparatus. They suggest the hypothesis that the organ of Corti with its related structures functions as a unit. By their concept "the pillars and phalangeal cells maintain a constant optimum pressure between the tectorial and basilar membranes, momentarily modifiable by movements of segments of the basilar membrane." Thus, stimulation of the hair cells can be brought about by increased pressure or by pulling the hairs attached to the tectorial membrane as the basilar membrane vibrates downward. They compare the sensitivity of the mammalian cochlea containing the tunnel space with the bird in which this structure is absent.

The repeated confirmation of Hallpike & Cairns' observation (11) of the association of dilatation of the endolymphatic system with Ménière's disease has provided additional evidence for Guild's conclusion (12) that the endolymph flows from the cochlea to the endolymphatic sac. Lindsay (13) has attempted to demonstrate the function of the endolymphatic sac in monkeys by studying the reactions of animals in which this structure had been surgically obliterated. In three animals in which there had been complete destruction of the sac and sinus II, there was no evidence of endolymphatic hydrops in the cochlea by histological examination. Also in none of the animals was there any evidence of disturbance of the equilibrium. This observation certainly casts doubt on the role of the endolymphatic sac as the organ for resorption of the endolymphatic fluid.

At the same time, Lurie's study (14) of the cochleae of the congenitally deaf collie and Dalmatian dog casts some doubt that the stria vascularis is the sole organ concerned with the production of endolymph. He found normally filled utricles and semicircular canals in dogs with complete degeneration of the stria vascularis. In spite of these researches, however, one is still faced with the

irrefutable evidence of increase in pressure of endolymphatic fluid which occurs in Ménière's disease. The suggestion of Altmann & Waltner (15) that resorption of endolymph may occur in the crista spiralis deserves attention but, at present, has little experimental support.

Kellaway (16) has been able to throw further light on the mechanism of the so-called electrophonic effect by studying the action of a combination of electrical and mechanical stimulation of the ear. The fact that patients reported hearing tones similar in frequency to that of an electric current applied to the ear seems to contradict our knowledge of the physiological behavior of nerves. Kellaway's studies showed: first, that beats developed when an an electrical and mechanical stimulus was applied to the same ear; second, that the sensations produced by two stimuli of different frequencies were similar with two mechanical stimuli or one electrical and one mechanical; and third, that when a mechanical and an electrical stimulus of the same frequency were applied to the ear, it was possible to cancel one by reversal of the phase of the other. Kellaway believes that this provides additional evidence that the electrophonic effect depends on the electric current's setting up mechanical vibrations within the ear as previouly suggested by Kahler & Ruf (17) and Stevens & Jones (18).

Acoustic Trauma

A number of papers have appeared, apparently stimulated by the War, on the effect of acoustic trauma on hearing. The results, in general, have shown that hearing loss following exposure to pure tones always affects frequencies higher than the stimulating tone, with the greatest effect about half an octave above. All the workers report diplacusis (19, 20). Davis *et al.* (19) claim this is most marked when the hearing loss is confined to a narrow band of frequencies. One can only feel that such findings should offer a clue to some of the basic physiological mechanisms concerned with hearing.

Function of the auditory nerve—Neff (21) and Wever & Neff (22) have studied the effect of partial section of the eighth nerve. Previous reports by Wever & Bray (23) and Dandy (24) have indicated that after partial section of the eighth nerve, one obtained either high tone loss or the total loss of response to all frequencies. Neff in his experiments conditioned cats to respond to

pure tones. Following partial section of the eighth nerve, the animals were retested. In about half of the animals, no hearing loss could be demonstrated. One third of the animals showed very marked high tone loss, while the rest showed complete loss. His results indicate that section of a small part of the nerve produces no demonstrable defect of hearing. Larger lesions affect only the high tones, the larger the lesion, the lower the frequency affected, but only down to a thousand cycles. He concludes that it is not possible to produce a hearing loss for frequencies below one thousand cycles without destroying almost the whole cochlear nerve. His explanation for the inability to cause low tone impairment by sectioning the eighth nerve is based on the multiple innervation of hair cells by each nerve fiber. In this concept, the hair cells subserving high tone response would receive innervation from a relatively few nerve fibers. He also concludes that the dips that are encountered clinically in audiograms must be the result of degeneration of the hair cells and not of nerve injury.

Wever & Neff (22) also attempted to correlate cochlear response measurements with histological findings using the same animals from the experiments previously described. They found the cochlear response measurements to be essentially normal in all the animals except one. The hearing of these animals as measured by conditioned reflexes ranged from normal to complete deafness. One cat which gave no sign of hearing to conditioned response tests showed marked high tone loss by cochlear potential measurements. Histologically there was extensive degeneration of a large proportion of the organ of Corti as well as the nerve. Their results indicate that extensive nerve cell atrophy in the basal coil impairs the hearing for high tones, but not for low tones, and that tones below one thousand cycles even at threshold intensity stimulate receptor cells over an extensive region of the cochlea.They conclude that there is some cochlear localization for high tones, but "far less specificity for low tones or even none at all."

Unfortunately none of the lesions produced in these experiments resulted in degeneration of apical turn nerve fibers exclusively. To this extent these experiments fail in answering decisively the problem of whether or not there is low tone localization. This is the same lack of information obtained in the correlation of hearing loss and post-mortem histological findings in patients studied by Crowe, Guild & Polvogt (25). It is hard to reconcile

the conclusions of Wever & Neff (22) with the disappearance of response in a localized region of the cortex following destruction of the organ of Corti in the apex reported by Walzl & Woolsey (26) and the tonal localization for pure tones in the medial geniculate body and the cerebral cortex reported by Licklider & Kryter (27).

Function of the higher auditory centers.—During the past few years, evidence obtained by a number of different techniques has been remarkably consistent in the picture presented of the internal organization of the higher auditory pathways. The techniques employed have included: (*a*) studies of degeneration of auditory radiation following lesions in the medial geniculate body and of retrograde degeneration in the medial geniculate body following lesions in the auditory cortex; (*b*) demonstration by oscillographic methods of localized loss of function in the cortex following small lesions in the medial geniculate body, and in the cochlea to total cochlear stimulation by click; (*c*) demonstration of localized response in the auditory cortex to short bursts of pure tones; (*d*) electrical stimulation of parts of the auditory nerve and auditory pathways including the auditory cortex; (*e*) strychninization of the auditory cortex and pickup of responses in other areas of the cortex; and (*f*) partial or total ablation at different levels of the auditory system and study of the effect on conditioned reflexes.

In general, these studies have led to the demonstration that there is an orderly projection of the organ of Corti maintained through intermediary pathways to the auditory cortex. The original experiments showed dual representation of each cochlea in each hemisphere with the parts of the cochlea represented in reversed order in the two areas.

Tunturi (28) has demonstrated the presence of a third auditory area in the dog, to both tonal and electrical stimulation of the cochlea. This area occupies about 10 to 20 sq. mm. of the cortex at the junction of the anterior ectosylvian gyrus with the coronal gyrus to form the anterior composite gyrus. Each cochlea has representation in each area, but there is little evidence of spatial tonal localization as in the other two areas. On the basis of masking and electrical stimulation of the cochlea, this author concludes that there are separate fiber connections from the cochlea to this area.

Ades & Felder (29) compared the sharpness of boundaries of

silenced areas in the auditory cortex following lesions in the medial geniculate bodies in cats, monkeys, and rats. They claim to have found sharp localization in the monkey, localization but with indefinite boundaries in the cat, and no response to click stimulation in the rat. They consider these findings to be consistent with Lashley's failure (30) to demonstrate localized areas of degeneration in the rat's medial geniculate body following cortical lesions. However, LeMessurier (31) has been able to obtain quite large responses (fifteen hundred to twenty-five hundred microvolts) from the rat's cortex by click stimulation. He also found an area that quite definitely corresponds to Tunturi's third auditory area. Preliminary experiments in co-operation with the author suggest also the presence of spatial localization of the cochlea in this animal.

The method of conditioned reflex auditory testing provides the closest approximation to the audiogram that can be obtained in experimental animals. However, the observations by a number of workers that the auditory cerebral cortex is not essential for conditioning to a sound makes it important to know which auditory functions can be subserved by each level of the higher brain pathways if the conditioning is to be used as a testing method. Rosenzweig (32) describes a method in which a change in intensity of sound is used as a stimulus for conditioning. In a few animals studied by him, either no change was obtained in thresholds following bilateral destruction of the auditory cortex or the response was reacquired with retraining. Raab & Ades (33) have used this same technique and have studied the effect of ablation of the auditory cortex and the superior and inferior colliculi. These authors observed that after bilateral destruction of the auditory cortex. retraining in intensity discrimination habit is necessary. Once retrained, the pre- and postoperative difference limens were essentially the same. In two animals, incomplete lesions were made and the conditioned habit was retained perfectly. This agrees with the findings of a number of other workers that the ablation must be complete to abolish the response. These authors found that in otherwise intact animals destruction of the inferior or superior colliculi had no effect on the conditioned habit. However, in animals with previous auditory cortex ablation, the reconditioning response was again lost after destruction of either the superior or inferior colliculi. It was possible to train the animal a third time,

but only with marked increase in difference limen. They conclude that in the cat there are at least three functional levels within the auditory nervous system: cortical, midbrain, and bulbar, and that the auditory cortex is normally concerned in the mediation of the learned responses to sounds, but that the lower centers are also capable of taking over the function if the cortex is destroyed. They also conclude that in animals in which the auditory cortex is removed, the relearning of the conditioned reflex is mediated by the inferior colliculi with the main efferent pathways proceeding through the superior colliculi.

The results of a number of workers have indicated that only a small part of the auditory area may be required for the maintenance of conditioned differential response to auditory stimuli. Unfortunately, knowledge of the exact boundaries of the auditory area was not available to many of the early workers who studied the effect of cortical ablation on conditioned reflexes. However, the definition of these boundaries by oscillographic studies now makes it possible to control more precisely the placing of lesions. Allen (34) in utilizing the data obtained by Tunturi (28) has studied the effect of ablation of the three auditory areas on conditioned differential response to sound in dogs. He found that bilateral removal of a single one of any of the areas had no effect. However, bilateral removal of areas I and II (or A and B in his nomenclature) caused loss of conditioned response, although this could be reacquired perfectly with retraining. With complete bilateral destruction of all three areas, conditioned differential responses could not be obtained even six months after the operation. He found no difference in the difficulty of conditioning previously untrained dogs and previously trained dogs after areas I and II had been removed. He suggests that this demonstrated the importance of these areas in the formation of sound association circuits.

Hampson (35), as part of a study of the projection of functional areas of the cerebral cortex onto the cerebellar cortex by oscillographic recording of evoked potentials, found that auditory areas I and II both project to the entire tuber vermis.

The fact that each ear has representation in each cortex is undoubtedly of importance in the determination of the direction of a sound source. Tunturi (36) has reviewed the evidence of the importance of phase difference and intensity difference in the two ears. He argues that localization by phase differences in the two

ears depends on a mechanism in the central nervous system capable of discriminating time differences. He undertook to demonstrate the presence of such a central nervous system circuit by studying the effect of two successive stimuli applied to the exposed osseous spiral lamina of each cochlea on the latency, absolute and relative refractiveness, and initial sign, of response in various levels of the auditory pathways. He confirmed the findings of Woolsey & Walzl (37) in the cat that responses at each cortical point to stimulation of homologous regions in each cochlea showed similarity in latency, duration, wave form, and initial sign. Studies with repetitive stimuli revealed an absolutely unresponsive period from 20 to 100 msec. in the cerebral cortex followed by a relative unresponsive period of 100 to 250 msec. These values were the same for stimulation of symmetrical regions of each cochlea. Similar values were obtained for durations of unresponsiveness in the radiations and medial geniculate body. The duration of periods of unresponsiveness to successive stimuli in the auditory pathways below the medial geniculate body was about 1 to 2 msec. From the fact that the unresponsiveness arises in the medial geniculate body, Tunturi concludes that there is a neurone common to both ears from the medial geniculate body to all three acoustic areas of the cerebral cortex.

Neff (38) has studied the role of the auditory cortex in the cat in the learning of a discriminatory response based upon the localization of sound in space. He found that such response was unaffected by unilateral ablation of the auditory cortex, but that bilateral ablation resulted in loss of the ability to make this response. He did find, however, that unilateral ablations caused decrease in the maximum time for correct delayed responses. Garner (39) has investigated the effect of changing the phase of pure tones in the two ears of humans. With change of phase all subjects reported a difference in apparent localization. Eighty per cent reported a change in pitch as well, while a smaller per cent thought there was a change in loudness. He suggests that the occurrence of apparent change in pitch with change in phase of the two ears may be related to the phenomenon of diplacusis.

Auditory testing.—The problem of distinguishing clinically between nerve and conduction types of deafness and of estimating the components of each in a particular patient has always presented serious difficulties. Von Békésy (40) describes a modification of the

measurement of the recruitment phenomenon of Fowler. He claims that the difference limen is diminished with nerve type deafness and that the measurement of difference limen will reveal commencing nerve deafness earlier than the hearing threshold itself. In a study of the recruitment phenomenon and its relationship to the difference limen in the vibratory sense, he concludes that the decrease of difference limen as a result of nerve degeneration would be less marked for low than high tones. This was actually found to be the case in audiograms made by this method. He also describes an ingenious method by which the patient is able to record his own audiogram and difference limen with an automatic recording device (41).

Gardner (42) has reported another clinical hearing test which he claims also aids in distinguishing between conduction and nerve deafness. In this method, a fatiguing tone lasting about two seconds is followed very quickly (20 to 50 msec.) by a short pulse (30 msec.) of slightly different pitch. On plotting the level of the secondary tone above normal threshold against the level of the primary tone, a curve is obtained, position and slope of which are characteristic for nerve and conduction types of deafness. Aside from the relative complexity of the testing, this method should have wider application than the loudness-balance method since it is applicable to the testing of patients with bilateral hearing impairment.

The problems of rehabilitation of people with hearing impairment is receiving considerable attention. Many of the techniques developed in the Armed Services are being carried over to civilian practice. The utilization of speech perception as a test of hearing is receiving special emphasis (43 to 46).

Although it has long been recognized that certain types of deafness are purely hysterical and that partial deafness may be aggravated by psychological tensions, the frequency with which this occurs has probably not been completely appreciated. The careful testing of personnel of the Armed Forces has shown how important it is to keep this factor in mind (47).

In the realm of therapy for deafness, the fenestration operation is still the subject of many papers. Keleman (48) has collected the literature on the fenestration operation and lists two hundred and sixty-three articles. A comprehensive and interesting survey of the field of "audiology" suitable for reading by the laymen has been

edited by Davis (49). This book also presents very clearly the problems of training and rehabilitation of the deaf. MacFarlan (50) has also summarized very briefly the problems of the congenitally deaf child and some of the techniques and treatments available for the training of such a patient.

The greatest stumbling block to early training of the congenitally deaf has been the difficulty of ascertaining the extent of the deafness and of estimating mental retardation due to this cause or that due to cerebral maldevelopment. It is essential, especially for speech development, that training be initiated at an early age. Up to the present it has been very difficult to obtain more than an approximate idea of hearing function in a child under three or four years of age. A recent report by Bordley, Hardy & Richter (51) suggests that a practical and reasonably accurate test of hearing in infants may now be available. They have made use of the technique of measuring the skin resistance to galvanic current which has been developed by Richter. The test procedure consists of applying pure tone test signals followed by faradic shocks. By this method a conditioned response is set up. A continuous record is then taken of the skin resistance. Each time the tone is sounded, there is a sudden shift in the skin resistance, apparently as a result of the psychological anticipation associated with the expected shock. According to the authors, thresholds obtained by this method agree almost perfectly with the audiogram. They have obtained apparently accurate results on children as young as eleven months. It is obvious that this technique will also be very useful in demonstrating malingering or in the study of patients with psychological overlay. Froeschels & Beebe (52) claim to be able to demonstrate hearing in new-born infants using Urbantschitsch's whistles. It will be interesting to see what thresholds are obtained by the conditioned method of testing in infants, especially in regard to the question of degenerative nerve changes in early life.

LITERATURE CITED

1. VON BÉKÉSY, G., *J. Acoust. Soc. Am.*, **20**, 227–41 (1948)
2. VON BÉKÉSY, G., *J. Acoust. Soc. Am.*, **19**, 452–60 (1947)
3. GALAMBOS, R., AND DAVIS, H., *J. Neurophysiol.*, **6**, 39–57 (1943)
4. VON BÉKÉSY, G., *Acta Oto-Laryngol.*, **35**, 301–15 (1947)
5. POHLMAN, M. E., *Ann. Otol. Rhinol. & Laryngol.*, **56**, 647–57 (1947)
6. KOBRAK, H. G., *Laryngoscope*, **57**, 247–55 (1947)

7. LICKLIDER, J. C. R., *Am. Psychologist*, **3**, 243–44 (1948)
8. GABOR, D., *Nature*, **159**, 591–94 (1947)
9. TUMARKIN, A., *J. Laryngol. Otol. (London)*, **60**, 337–68 (1945)
10. LARSELL, O., MCCRADY, E. J., AND LARSELL, J. F., *Acta Oto-Laryngol.*, **40**, 233–48 (1944)
11. HALLPIKE, C. S., AND CAIRNS, H., *J. Laryngol. Otol. (London)*, **53**, 625 (1938)
12. GUILD, S. R., *Am. J. Anat.*, **39**, 57 (1927)
13. LINDSAY, J. R., *Arch. Oto-Laryngol.*, **45**, 1–13 (1947)
14. LURIE, M. H., *Laryngoscope*, **58**, 279–87 (1948)
15. ALTMANN, F., AND WALTNER, J. G., *Ann. Otol. Rhingol. & Laryngol.*, **56**, 684–708 (1947)
16. KELLAWAY, P., *J. Neurophysiol.*, **9**, 23–31 (1946)
17. KAHLER, O., AND RUF, C., *Z. Hals Nas. Ohrenheilk.*, **29**, 218–30 (1931)
18. STEVENS, S. S., AND JONES, R. C., *J. Acoust. Soc. Am.*, **10**, 261–69 (1939)
19. DAVIS, H., MORGAN, C. P., HAWKINS, J. E., GALAMBOS, R., AND SMITH, F. W., *Federation Proc.*, **5**, 22 (1946)
20. RUEDI, L., AND FURRER, W., *Acta Oto-Laryngol.*, **33**, 460–70 (1946)
21. NEFF, W. D., *J. Comp. Physiol. Psycol.*, **40**, 203–15 (1947)
22. WEVER, E. G., AND NEFF, W. D., *J. Comp. Physiol. Psychol.*, **40**, 217–26 (1947)
23. WEVER, E. G., AND BRAY, C. W., *J. Psychol.*, **3**, 101–14 (1937)
24. DANDY, W. E., *Bull. Johns Hopkins Hosp.*, **55**, 240–43 (1934)
25. CROWE, S. J., GUILD, S. R., AND POLVOGT, L. M., *Bull. Johns Hopkins Hosp.*, **54**, 315–79 (1934)
26. WALZL, E. M., AND WOOLSEY, C. N., *Bull. Johns Hopkins Hosp.*, **79**, 309–19 (1946)
27. LICKLIDER, J. C. R., AND KRYTER, K. D., *Federation Proc.*, **1**, 51 (1943)
28. TUNTURI, A. R., *Am. J. Physiol.*, **144**, 389–94 (1945)
29. ADES, H. W., AND FELDER, R. E., *J. Neurophysiol.*, **8**, 463–70 (1945)
30. LASHLEY, K. S., *J. Comp. Neurol.*, **75**, 67–121 (1941)
31. LEMESSURIER, D. H., *Federation Proc.*, **7**, 70–71 (1948)
32. ROSENZWEIG, M. J., *Am. J. Psychol.*, **59**, 127–36 (1946)
33. RAAB, D. H., AND ADES, H. W., *Am. J. Psychol.*, **59**, 59–83 (1946)
34. ALLEN, W. F., *Am. J. Physiol.*, **144**, 415–28 (1945)
35. HAMPSON, J. L., *Federation Proc.*, **7**, 50 (1948)
36. TUNTURI, A. R., *Am. J. Physiol.*, **147**, 311–19 (1946)
37. WOOLSEY, C. N., AND WALZL, E. M., *Bull. Johns Hopkins Hosp.*, **71**, 315–44 (1942)
38. NEFF, W. D., *Am. Psychologist*, **3**, 243 (1948)
39. GARNER, W. R., *Am. Psychologist*, **3**, 243 (1948)
40. VON BÉKÉSY, G., *Laryngoscope*, **57**, 765–77 (1947)
41. VON BÉKÉSY, G. *Acta Oto-Laryngol.*, **35**, 411–22 (1947)
42. GARDNER, M., *J. Acoust. Soc. Am.*, **19**, 178–90 (1947)
43. HUDGINS, C. V., HAWKINS, J. E., KARLIN, J. E., AND STEVENS, S. S., *Laryngoscope*, **57**, 57–89 (1947)
44. KEASTER, J., *J. Speech Disorders*, **12**, 159 (1947)
45. HARRIS, J. D., *Arch. Oto-Laryngol.*, **44**, 452–67 (1946)

46. CARHART, R., *J. Speech Disorders*, **11**, 97–108 (1946)
47. SEMENOV, H., *Eye, Ear, Nose Throat Monthly*, **26**, 326–48 (1947)
48. KELEMAN, G., *Laryngoscope*, **58**, 74–85 (1948)
49. DAVIS, H., *Hearing and Deafness*, 496 pp. (Murray-Hill Books, Inc., New York, 1947)
50. MACFARLAN, D., *J. Am. Med. Assoc.*, **137**, 774–75 (1948)
51. BORDLEY, J. E., HARDY, W. G., AND RICHTER, C. P., *Bull. Johns Hopkins Hosp.*, **82**, 569 (1948)
52. FROESCHELS, E., AND BEEBE, H., *Arch. Oto-Laryngol.*, **44**, 710–15 (1946)

VISION

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The present review covers the period July, 1947 to June, 1948, plus earlier papers not previously reviewed. Returning normal scientific conditions has restored access to a growing foreign literature, facilitated by two new review journals (1, 2). Results from the war years have just been organized (3). These, with other expert summaries (4) in the subdivisions of our topic, impel the reviewer to comprehensiveness rather than criticism. The number of papers in relation to available space suggests a compromise, giving the reader some organization and evaluation, yet arbitrarily citing but one point from each paper and omitting about fifty. A rather clipped style then affords a slight expansion on visual physiology (see p. 250), and on those broader syntheses which add connectedness to the piecemeal observations. Our field suffers this year by losing the personal stimulus and work of Selig Hecht [for obituary notices, see (5, 6)].

VISUAL APPARATUS: ANATOMY AND VEGETATIVE FUNCTIONS

General

A major contribution to the comparative anatomy, embryology, and paleontology of the eye is Rochon-Duvigneaud's book (7). The section on man is less original. His treatment is thorough, but less than Walls' on visual function. Nageotte analyzes dioptrics in arthropod vision, especially that of the blue fly (8). Von Sullman reviews (9) ocular biochemistry (1942–1946) in German.

Cornea and uvea.—Taylor (10) discusses progress in knowledge of the cornea. Specific amino acids are needed in metabolism [Sydenstricker *et al.*(11)]. Carbon dioxide may pass both ways, but oxygen is supplied from within [Bakker (12)]. These considerations affect the fluids used with contact lenses (13). The transparency of the peculiar fibrous structure of the cornea (14) depends on dehydration and other conditions [Hart (15)]. However, the cornea does absorb and scatter some light unselectively [Maxwell *et al.* (16)].

Matteucci traces the sympathetic and parasympathetic innervation of uveal circulation (17), finding it is in parallel with the cerebral control. Vasoconstrictors in the iris (Langworthy) are absent (18).

Lens (see also p. 249).—Electrophoretic studies [Viollier *et al.* (19)] of the water-soluble lens proteins measure the excess of α- over β-crystallin; but the latter is complex in young animals and lower forms (20). An halloxazine, rather than flavin, causes fluorescence in the lens (21).

Aqueous and Vitreous

Regarding the external control of ocular tension, Fradkin (22) finds a sympathetic path from the premotor cortex, but Schmerl (23) locates it diencephalically, by comparing anesthetics. Panzardi's work (24) agrees. Magitot discusses the psychosomatic mechanism (25) which may act as well through endocrine effects that Radnot (26) demonstrates. Strenuous exercise may act through such factors in affecting ocular tension (27).

As regards local vascular control, the uveal veins respond little to lower carotid pressure, failing to regulate outflow according to inflow [Bárány (28)]. The pressure here (50 mm. Hg) suggests a diffusion mechanism [Sondermann (29)]. Capillary diffusion as affected by vasoconstrictor drugs may be measured *in situ* by the Tyndall effect (30). The retinal vessels, in contrast, offer a barrier (as in choroid plexus) impermeable to vital stain [Palm (31)].

Vitreous.—Davson & Duke-Elder draw attention to the vitreous exchange as a regulating factor in intraocular pressure (32). This is confirmed by Hupsel, who crystallized a ciliary-body fraction which alters the vitreous volume (33).

Fluid flow.—Dynamic equilibria of aqueous constituents are being measured. A light-scattering method of Huber determines the protein fraction (34). Vanzetti finds glucose lower than in serum, but chlorine the same (35). Ethyl alcohol also penetrates freely (36). Sodium is higher than in serum, almost reversing the Donnan ratio, a fact which suggests to Scholz *et al.* a secretory process (37) that is extremely rapid (38). The relative penetrations of sodium and chlorine deny the analogy of aqueous secretion to that of the choroid plexus (39).

Studying the inflow mechanism, Davson & Duke-Elder (32) show that reducing sugars (*vs.* sucrose) diffuse in rapidly, but are

kept low by retinal metabolism which is discussed by Krause (40). Kinsey shows that the secretory control for ascorbic acid develops late (41). The effects of drugs on tension seem to operate also via the osmotic inflow [Bárány (42)]. In this regard, rutin does not alter permeability, but blocks physostigmine action [Stocker (43)].

In the outflow mechanism, DeVries describes the aqueous vein system in detail (44). Davson discusses Bárány's theory of osmotic *vs.* hydrostatic control (45). They collaborate on a clarification of secretion *vs.* diffusion (46).

Retina

At the ora serrata there is a band of receptors 2 mm. wide, 7 mm. from the cornea, accessible to light transclerally, but not through the pupil [Druault (47)]. The refractive index of the ungulate retina, 1.3610, drops in dark-adaption due to aqueous shifts from photochemical hydrolysis [Ajo (48)]. Vilter describes the retina of a fish (*Callionymus*) which is organized with the rods below, and the cones and cone-bipolars above (49). In the guinea pig, O'Day cites cone structure, rod-cone ratio, and nuclear ratio favoring day-vision (50). Granit now verifies this physiologically (51). Hartridge remeasures Poliak's pictures of foveal cones, finding 4 μ the least diameter (52), nearer Osterberg's estimate (2. 6μ or 0.5′)than Poliak's of 1 μ.

The retinal vessels have capillary sphincters, sensitive to epinephrine (53). At high altitudes (anoxia) the vessels distend (54),especially at branch points (55), but collapse in some cases (56). The muscae volitantes, a vascular effect, may now be plotted accurately (57).

Sensory Nerve Paths: Anatomy and Nutrition

The blood supply of the optic nerve is reviewed in detail by Vail (58). Optic nerve atropy (blurring and scotoma) can result from starvation diets apart from vitamin deficiency (59). Recent data on sensory nerve (60) suggest that vitamin B_1 should strongly affect at least the initial neuron. Nauta & Van Straaten, tracing bouton degeneration in the rat, find in the thalamic pulvinar a nucleus homologous to the lateral geniculate (61), which, however, connects the retina to the second visual cortex (62). Solnitzky & Harmon discuss layer IV of the primate visual cortex (potto, galago, man) (63).

VISUOMOTOR SYSTEM: STRUCTURE AND FUNCTION

Extraocular Muscles: Neurology

Cogan's brief illustrated text on neurology (64) also covers current anatomy and physiology. The experiments of Hoessly (65) find a basis for the fixation reflex of the cat in topical projection on the colliculus as shown by Marchi method. Crosby & Henderson (66) demonstrate on the monkey tectum an efferent (muscle) localization. Accurate regeneration of severed oculomotor fibers fails at the late larval stage even in amphibians [Sperry (67)].

Visual function.—A thorough treatment of general relations and functions appears in chapters 2 to 6 of *Oculorotary Muscles* by Scobee (68), who also writes a critical review (69). The more abstruse balances in pure torsion are discussed by Tschermak-Seysenegg (70). For practical diagnosis and specification, a committee (71) recommends referring torsions to a new axis. An unusually simple device for visuomotor measurements is described by Pacalin (72).

Intraocular Muscles: Pupillary Reflexes

Thorough studies of pupillary kinetics still wait adequate recording in the dark. The snooperscope [Koomen *et al.* (73)] may revive Braunstein's photochoreograph. Quantitatively, Corrado shows sensitivity to vary with log area in the fovea (74). A suprathreshold binocular stinulus proves over twice as effective as the monocular [Thomson (75)]. In dark adapting, initial diameter determines the course of dilation [Wagman (76)].

The pupillary light-threshold yields to cortical suppression in physiological rivalry, via corticoretinal paths [Bárány (77)] (not corticomotor). The light-reflex, passing via the tectum, apparently escapse narcosis by pentothal (24). The pain reflex is parasympathetic also [Kuntz & Richins (78)].

Intraocular Muscles: Accommodation

To the general relations of the choroid layer, ciliary muscles, and zonula [Wolff (79)], Layton *et al.* add a new mechanism: a vasomotor hyperopic action of the ciliary body, like Langworthy's pupillary dilator (80). Yet paralysis of sympathetic reduces neither speed nor range of accommodation [Matteucci & Toselli (81)]. In accommodation, the lens gains as much power by changes

in density as in curvature [LoCascio & DeLeonibus (82)], confirming Gullstrand. Asymmetric contraction of the ciliary body accounts for an increase in astigmatism [O'Brien (83)].

Significant training in precision of accommodation does occur [Brozek *et al.* (84)]. Dubois-Poulson, by exercising accommodation, produced recession of nearpoint (plus nervous exhaustion), independently of illumination (85).

Night myopia.—Interest in the adjustment of night glasses led Wald to basic experiments and a summary (86). Supplementing chromatic error (0.5 D) from the Purkinje shift (87), relaxed accommodation leads to widely variant ametropias (86). Schober's explanation that larger blur-circles favor scotopic vision (88) is denied by data of Chapanis (89) and Wald. The 1.5 D (relaxed) myopia of outer pupillary zones seems important [Ivanoff (90)].

Refraction (see also p. 248)

A joint investigation of the evidence for reducing myopia has convinced optometrists (91), as well, that training does not yet affect the control of dioptric mechanisms (92). Hirsch & Weymouth calculated the partial correlations between the optical elements in Stenström's data showing that these elements are in general so combined as to cause the over-all refraction of the eye closely to approximate emmetropia (93). Deller *et al.*, using three (x-ray) diameters, also relate refraction and eye-volume (94). We need such length measurements in children with increasing myopia.

Dioptrics.—Jaeger shows types of barrel distortion, rarely discussed (95). Spherical aberration amounts to 1.1 D between central and outer zones [Koomen *et al.* (96) and Ivanoff (90)]. The increasingly important dioptrics of the aphakic eye are described by Pascal (97). In astigmatism, hereditary factors control the axis [Biro (98)].

In addition to summated errors, we have inhibition between blur-circles [Weidmann (99)], insensitivity to color fringes (100), and micronystagmus (190). Hence, the Gaussian affords a simpler and closer approximation to the over-all blur effect than the Bessel diffraction curve [Fry (101)].

Method.—Le Grand & Guillemot (102) discuss blurring measures of acuity and the variability of the Snellen chart. For malingerers, the optokinetic threshold (seen ophthalmoscopically) readily measures acuity [Pfister (103)]. Gát describes an accurate measure of astigmatic axis and error by Scheiner's method (104).

Oculovestibular Relations

An otolith modification of periodic eye movements results from tilting the head both in caloric (105) and in postrotatory nystagmus (106). Henderson finds that optokinetic nystagmus dominates the postrotatory type, along with cortical influence (107). However, Copazzi & Sala show optokinetic to suppress caloric nystagmus, but not the postrotatory. The release of caloric stimulus facilitates the optokinetic (108). Oscillation of a retinal after-image in vestibular nystagmus suggests kinesthesia from eye-muscles [Göthlin (109)].

VISUOSENSORY SYSTEM: NONVISUAL OBSERVATIONS AND MECHANISMS

Receptor Physiology: Pigment Chemistry

Both rhodopsin extract and vitamin A are now shown to be readily convertible to retinenes *in vitro* [Wald (110)]. Bliss emphasizes the enzymatic aspect of the rhodopsin-vitamin A reactions (111). Ball *et al.* show many synthetic complexes of vitamin A aldehyde fitting the definition of retinene and regard retinenes as extraction artefacts, not in the visual cycle (112). The synthesis of vitamin A_2 [Morton *et al.* (113)] shown present in vertebrate retinas (114)may correlate with human color vision.

Cephalopsin (in squid) shows that a light reaction may be independent of photolysis [Bliss (115)]. Is it independent in rhodopsin also? Galloxanthin, another nonphotolytic carotenoid (114), occurs in avian retinal droplets (116).

Besides rhodopsin, receptors contain much phospholipid nearly protein-free and independently extractable [Ishimoto & Wald (117)]. Pure rhodopsin also has heavy lipid fractions, little known, whose linkage to the carotenoid may cause transient orange, and the "positive blue" effect (199, p. 252).

Electric responses.—In the dark adaptation of limulus [Hartline & McDonald (118)], pre-exposure approximates the reciprocity law and affects the course roughly as in man. The number of spikes follows (suprathreshold) intensity by $N = a + b \cdot \log I$, but not so frequency (which governs the next synapse). Apparently other receptor properties than sensitivity vary with the adaptive state (119). [In humans, the pre-exposure law defies simple formulation

(120) and other adaptive functions are superimposed on the slow one (195, p. 279).]

Limulus receptors respond to small differentials of intensity by the law $\Delta N = K\Delta I/I$; again frequency is less simple [MacNichol & Hartline (121)]. Craik explored such transients visually. A photochemical theory for transients in limulus indicates that the reactan must have an inactive fraction [Fry & Alpern (122)]. In limulus the depolarizing current causing fiber discharges may be the corneal action current, but not surely [Hartline (123)]. In the grasshopper, receptor spikes seem true discharges, not electrotonic [Wulff & Jahn (124)]. Limulus shows both.

Optic-Nerve Physiology (Postbipolar, Single Fiber)

The bipolar network adds various enzymatic cycles, e.g., acetylcholine (125) and the supporting glycolysis (40) whose kinetics should affect visual behavior. Spikes from single optic fibers yield large and constant voltage, involving electrotonic components [Gernandt (126)].

Spectral tests show that rods dominate *on*-fibers, while an *off*-response characterizes cone contribution. However, rod-*vs*-cone contributions to the same optic fiber may shift during adaptation [Granit & Tansley (127)]. A new method, using polarization and threshold ratios, stabilizes chromatic data from single fibers. The *on*, *off*, and *on-off* fibers are subgrouped by response to anodal and cathodal stimuli [Gernandt & Granit (128)]. Granit's analysis of the interaction between electric and photic stimuli brings out the contribution of retinal interneurons to inhibition in the spike pattern (129).

Chromatic response.—The anodal and cathodal types of *on-off* fibers are differently color-sensitive [Gernandt (130)]. Combined electric and photic stimulation shows *on*-discharges peaking at one wave length, *off*-responses near the complementary [Gernandt (131)]. Such a single fiber carrying complementary qualities, e.g., by positive and negative frequency modulation, would be most important to visual theory and general neurophysiology. However, Gernandt regards the *on-off* fibers as twinned (126). Granit shows in the cat chromatic excitabilities of fibers (polarized) to peak near 460,520,610 mμ. He emphasizes that the "modulator" peaking is not in receptors but is only postbipolar (132), contrary to most

interpretations (248, 199). In effect, the bipolars cause a transformation of color coordinates, as in Müller's theory (133).

Human Electroretinogram

This observation (representing rod-cell, bipolar, and possibly ganglion cell potentials) reveals scotopic function in the presence of photopic [Riggs (134)], and is used by Monnier for peripheral-central comparisons (135).

Higher Levels

Degeneration in the geniculate of monkeys kept in blue light confirms color representation there [Clark & Chacko (136)]; but representation of the fovea on both cortices is again denied [Austin *et al.* (137)]. Conduction time, taken from retinogram and encephalogram, may measure pathological states in optic paths [Monnier & Jeanneret (138)]. Cohn's ingenious theory clarifies the phase-shifts in alpha activity (139). Controlling these by photic drive may trigger an epileptic focus [Cobb (140)].

Nonphotic Stimulation: Mechanical and Electrical

The dark center in a pressure phosphene is explained by Corrado (141). Barnard demonstrates "electric images" (phosphenes as small as 2°), suggesting applications (142). Barlow *et al.* report the static and transient effects of light adaptation, which raises the electric threshold (143). With alternating currents, the frequency effect indicates that stimulation operates not on receptors but neural elements, periodically facilitating the adapting light [Schwartz (144)]. This recalls Gernandt's work. The available alternating magnetic fields (one frequency) only stimulate achromatic peripheral response (145): rod pathways.

Higher stimulation, nonphotic.—Estaban mentions drugs that evoke false perception of colors (146). Irritation of area 17 causes flashes and fireballs; of area 18 and 19 color sense [Frantz & Vogel (147)]. Physiologically extraordinary is an occipital inflammation causing hemeralopic deuteranopia [Schober (148)].

SIMPLER SENSORY OBSERVATIONS AND THEORY

Light Sense at Lowest Adaptive Level; Threshold Variants

It is reported by von Studnitz that sensitization results from vitamins A and C, but not B_1 or lactoflavin (149). However, Rose &

Schmidt found such changes by vitamin A and several other agents to be within normal variation (150). In A-deficient subjects, Sheard correlated visual thresholds with actual serum vitamin A levels (151); any accompanying contraction of fields would escape ordinary perimetry [Sloan (152)]. Excess vitamin B_2 lowers visual thresholds (153) but deficiency causes photophobia (154) and higher thresholds (152). Increased pulmonary pressure raises rod thresholds more than cone (155). Without effect on thresholds are sulphanilamide in clinical doses (156) and cytochrome-*c* (157). Chapanis reports an optokinetic adaptometer (158).

Long-wave thresholds, corrected to the standard luminosity curve, are determined to 1050 mμ, foveally and peripherally. Luminous threshold energy here equals cutaneous heat sense, but red color persists [Griffin *et al.* (159)]. The intrinsic infrared energy in the eye, far subthreshold, equals threshold energy at 500 mμ [Pirenne (160)].

Transient light sense thresholds just before and after a flash vary greatly between individuals. The anticipatory rise is curious [Crawford (161)].

Light sense, directional.—The concentration of light in O'Brien's model of cone structure increases their efficiency tenfold. Polarization is negligible (162). The directional effects fit the basic data [Platt (163)]. These effects enhance cone sensitivity in the peripheral retina [Flamant & Stiles (164)].

Light sense, analytical data.—The scotopic luminosity-area function follows Ricco's law ($B \times S = \text{const.}$) on mixed receptors, up to 10′ to 25′ diameters [Brown (165)]. For rods these limits become 30′ to 50′, and for cones 6′ to 30′: fitting a population-density theory of functional units [Haig & Haig (166)]. At 15° peripherally for rods $B \times S = \text{const.}$, but for cones $B \times S^{-1} = \text{const.}$, a difference explained by retinal organization [Baumgardt (167)].

At higher adaptive levels, binocular addition [Ivanoff (168)] departs from Ricco's law. If also test is unequal to surround, liminal test steps depend more on ratio than adaptive level [Wallach (169)].

The luminosity-duration function follows reciprocity ($B \times T = \text{const.}$) for all wavelengths [Galifret & Pieron (170)]. Both reciprocity laws fail at intrinsic areas (2′) and times (40 msec.) such that the test-spot first acquires subjective area and duration [Jalavisto *et al.* (171)]. As regards the first suprathreshold step, in-

tensity has twice the effect of duration [Reenpää (172)], again an intrinsic time.

Light sense threshold, fluctuation theory.—In 1932 Barnes & Czerny determined the intrinsic (Poisson) fluctuation of quanta around the average number just visible. Using this experiment Brumberg *et al.* (173), Hecht *et al.* (174), and Van der Velden (175) separately found the number needed for vision. One value (five to seven quanta) agreed with data on visual purple. Three independent experiments of Van der Velden, two more discriminating (176) than the other (174), amply confirmed and extended by Baumgardt (177), showed exactly two quanta sufficient.

With this value, resting on a "critical" time and area (independent of photopigment concentration) one can measure the concentration of visual purple in an observer's eye (178). Results agree with data of Hecht and deVries (179). The "critical time" spans the subliminal excitation (from one photon) at the synapse gathering from a "receptor group," a functional unit which defines a "critical area" varying with type of receptor, retinal location, adaptive level, all empirical. Ten Doesschate (180) discusses the size and distribution of such units. Baumgardt (177) shows that visual purple may determine adaptive levels but cannot govern threshold differentials, however aptly such theories fit. At higher adaptive levels, brightness and acuity threshold also depend on critical areas and times, somewhat larger than before [Bouman & Van der Velden (181)].

As excitation depends on subliminal synaptic summation [Baumgardt (177)], threshold frequencies will vary with frequency. Thus the sensitivity varies with the intensity differential, as required by the transition (near threshold) from linear to log law at all adaptive levels. On entirely different grounds, Rose proves such an amplifying (slope-changing) mechanism must supplement visual purple (182). Baumgardt also shows the relation of micronystagmus, retinal inhibition, and periodic after-images (183).

The present quantum arguments postulate some fixed number, exceeding which stimulation always occurs. This condition need not exist; the "threshold quantum" (seen through N synaptic levels) may vary also (173). Even if exactly two are "needed" and five "fit" (174), the discrepancy is a biological variation (Baumgardt (177)], exceeding the physical (cf. 270).

Other Thresholds; Angle Acuity

Reimert (184) reports distance and angle acuity at dusk 1 to 300×10^{-4} ml. Hecht *et al.* determine the minimum dark-line (0.51″) and square (22″) visible against sky at 1 and 4×10^{3} ml. (185). Martin & Kaniowski measure (gun) flash acuity (angle × duration *vs.* brightness), a law linear only for mid-angles (186). At threshold, brightness-contrast *vs.* angle-acuity shows no simple relation [Hendley (187)]. One considers cortical factors: acuity goes while light sense stays, in strabismic amblyopia (188); also monkeys kept dark till grown have light sense, not acuity (189).

Graininess acuity.—Among physiological cues, micronystagmus alone detects (dynamically) the 0.2 per cent limen in photographic granularity [Jones & Higgins (190)]. Syzegetic averages enhance granularity, when recorded by a scanning aperture, adjusted subjectively. Unlike angle acuity, graininess increases at low brightness (191).

Flicker acuity.—Fusion frequency drops in old age [Misiak (192)]. Used campimetrically, critical fusion frequency (c.f.f.) detects latent scotomas from tobacco neuritis [Roussel & Weekers (193)]. Occipital wounds lower the c.f.f. and distort apparent and actual motion [Teuber & Bender (194)]. Tridione reduces c.f.f. at high brightness, with other retinal inhibitory effects [Sloan & Gilger (195)].

Border and contrast acuity.—Photopic visibility of rectangles brighter than the surround depends on the flux in a one minute borderstrip [Lamar *et al.* (196)], confirming studies by Fry (197) on more complex edges, darker than surround. This important result, unexplained by retinal illumination gradients, correlates Ricco's law, critical distance (181), etc.

Indirect Light Adaptation; Light Sense

Of various glare colors, blue most affects neighboring thresholds [Ivanoff (198)] (luminosity uncontrolled). The rapid recovery rate after indirect adaptation varies with pre-exposure, but (except for α-adaptation) light sense thresholds do not rise while the light is on (199, p. 227).

Angle-acuity also falls near both dark (200) and bright objects. Schouten's glare formula describes this, as well as contrast at

sharp or blurred borders [Fry (201)]. Some of these effects are interocular (cortical) (200). Chromatic sources (luminosity uncontrolled) also induce acuity changes (202).

Acuties in Peripheral Vision; Light Sense

Comprehensive data on normal threshold range *vs.* angle show incidentally that rods and cones share equally at the 0.7 ml. level [Sloan (152)]. The scotopic limits contract with age (203). A naive industrial test is given (204).

Angle acuity.—This improves with exposure-times, to over 1 sec. at 60° [Low (205)]. From 25° to 50° peripherally, the photopic to scotopic acuity remains 16:1, regarded as the rod-cone ratio [Scott & Solandt (206)]. Scotopic acuity, unlike population or light-sense, is constant 4° to 30°. At higher adaptive levels, acuity peaks near 6°. Well above cone-thresholds, rod acuity dominates [Mandelbaum & Sloan (207)].

Other acuities.—Guggenbühl measures the depth-range, photopic and scotopic, to 90° by Monje's method. The photopic-scotopic ratio is small (208). Depth-acuity, like angle-acuity, is greater peripherally in the lower fields [Gaus (209)]; but relief can barely be seen to 20° [Plicque (210)]. Motion acuity drops rapidly from 30° to 60° [Low (211)]. Scotopically also, motion and displacement thresholds rise from 6° to 60° [Gordon (212)]. Clemmeson describes thickness discrimination, aligning power, and other peripheral functions under unusual conditions (213).

MOTION, SPACE, COLOR AND HIGHER SENSES

Motion Sense and Apparent Motion

The scotopic threshold for motion is four times the photopic [Hodel-Boos (214)]. Liang & Pieron apply the binocular pendulum to various latency *vs.* brightness functions (215). Goldmann notes that the assymmetrical spread of angioscotoma with pressure depends on motion of the test-object. A visual experiment, independent of blood vessels, shows that retinal latencies are involved (219).

Graybiel *et al.* show an oculogravic apparent motion (216) governed by radial acceleration and tilt; also an oculogyric "illusion" (217). By a "negative" apparent motion with changing "g," a moving pendulum appears vertical (218). Mechanical relativity contributes to this apparent aperiodic "nystagmus."

Space Sense; Depth Acuity

Under test conditions (Harvard University) stereoacuity is unaffected by posture, reduced blood pressure (220), exercise, or startling; it is reduced by hyperventilation, oxygen excess, and increased by metrazole (221). Chromatic error has widely variable effects on stereoacuity (222). Stereo- and angle-acuity correlate closely and vary similarly with illumination [Hirsch & Weymouth (223)], but haze affects coincidence settings more than stereo (224).

The (angular) depth of fusion at one meter is now standardized (225). With increasing distance, larger (angular) targets aid depth of fusion (226). Strength of fusion, measured by reaction-time after a standard stress, determines the observer's stability (227), a rather complex suprathreshold criterion.

For depth perception, Smith (228) finds double images are sufficient stimulus (flash technic). Scalar data and attention to other cues would strengthen such denials of the dynamic theories of fusion (229).

Levels of integration; lateral disparity.—Even with sensory fusion, stereopsis may fail (210) as in anomalous correspondence [Burian (230)]. By alternating suppression, sensory fusion may fail also, leaving only motor fusion, which still shows a range (231). Tests of degree of correspondence vary, the most stringent being the after-image (232). The pseudomacula may be used alternately with true correspondence (233).

Size disparity.—Suppression can obviate the aniseikonia (1.5 per cent per diopter) from large refractive difference (234). Below 1.75 per cent size difference, the cortical contribution subject to psychoneurosis is most common (235).

Space sense, indirect adaptation.—The figural distortions, induced near a previously fixated image, apply also to depth, which therefore would be a true sensation [Köhler & Emery (236)].

Space perception; distance and shape.—Apparent distance, unlike depth acuity, is unaffected by target size (237). Furthermore, apparent shape is unaffected by certain variations of physical shape [Stein (238)]. The apparent curvature of straight lines, qualitatively involving perspective, etc. (239), follows a quantitative relation between physical and subjective space such that translated shapes are invariant in the (mathematical) transform. Ex-

periment proves this psychophysical space hyperbolic, with horopters as geodesics. A simpler summary (240) follows Luneberg's original paper (241).

Color Vision, Anomalous Tritanopia in Fovea

The weakness of blue sense in the fovea (242) discovered by Hering (1893) was shown by Thompson & Wright (243) to yield the neutral point, reduced short-wave discrimination and characteristic red-green colors of tritanopia. However, the reduced short-wave luminosity, brighter red (causing anomaloscope errors) (244) and variation with intensity (245) are anomalous for this dichromasy (199, p. 334). Toward the foveal edge, blue increases, red decreases; but some blue deficiency remains with small fields (243). This suggests larger receptive units for blue than for red-green. Hartridge found small-field red enhanced peripherally also (246). The dependence of color components on test-area extrafoveally has not been studied.

The changes with intensity (reverse Purkinje shift) recall Stiles 1° test data (247) showing foveal blue receptors have high thresholds, departing as sharply from the red-green system as do the latter from rods. Hartridge finds this "antichromatic response" in blue more than compensates the chromatic aberration of the eye (100). By microinduction methods Hartridge (248) shows a a selective peak for yellow, located at a dip in the luminosity curve (245) [and also on the blue-sense curve of Stiles (247)]. Such gradients (angle, area, meridional, and intensity) in blue sense make the "normal" trichromasy an artefact of the "normal" test field [Thompson (243)].

General dichromasy.—Although American isochromatic tests successfully screen dichromats (249), like the Ishihara (250) they do not grade or classify. The Swedish tests have similar weakness (251). Volk & Fry show the error of observing such tests parafoveally (252). Training in the AOC test improves score on this only (253), but training on the Dvorine appears transferred (254). Pickford's anomaloscope test for protanopes is new (255).

In general, inherited dichromasy is not associated with pigmentation in whites [Pickford (256)]. Among animals, protanopia in Cebus monkey is confirmed [Malmo & Grether (257)].

Color mechanism, theoretical.—The luminosity curves of protans and deutans [Hecht & Hsia (258)] show that their receptors (or

those of tritanopes or anomalous trichromats (199) can be neither loss nor collapse systems. This destroys a fundamental postulate of the primaries proposed by Szekeres (259), as well as König, Helmholtz, etc. DeVries' bunched receptor system (260) seems incompatible with acuity data. Prentice, however, has improved the experimental basis of cortical yellow (261).

Indirect adaptation.—A red-green blind (protan or deutan) sees a curious luster at the junction of red and green fields (262), possibly a combination of Mach effect (201) and color stereoscopy [Wagenaar (263)].

Trichromatic theory and color adaptation.—Wright's book (199) summarizes present knowledge and problems, adding new material on physiological relations, chromatic adaptation (direct and indirect), dichromasy, and the nature of thresholds. Removed from standard conditions, the rules underlying mixture equations show serious discrepancies. The fundamental response curves prove changeably coupled; "basic" primaries vary with area and location. The psychophysical method is patently inadequate.

During adaptation of colors from daylight to incandescent, orange and indigo prove invariant [Helson & Grove (264)]. Such reference of data to the adaptive level rather than zero sensation, Helson regards as fundamental in all psychophysics (265). Already formulated for color vision (266), this principle applied to physiology would suggest scaling inhibitions like sensations.

Higher Visual Functions; Visual Fatigue

The empirical correlation of blinking with subjective fatigue (267) is shown not a measure of visual work (268) or efficiency [Bitterman & Soloway (269)]. Lawson finds the "blackout ratio" surprisingly high in blinking (38 to 69 per cent), a significant fluctuation in visual measurements (270). Neither the battery of fatigue tests of Simonson *et al.* (271) nor any other optical or mechanical measure is sensitive to visual as distinguished from "general" fatigue [Carmichael & Dearborn (272)]. Indeed, some psychic conflict seems necessary [Bartley (273)].

Illumination in reading.—Hoffman (274) finds Luckiesh's own data indicate a 15 fc. optimum (*vs.* 100 fc.); but performance tests show optima near 100 fc. [Simonson & Brozek (275)]; fusion-frequency, eye-movement, and recognition-time vary with illumination. Martin & Pearse (276) find "ease of reading" better with red

light (cone-vision). Illumination correlates poorly with vision anyhow; in practical lighting, an integrated "brightness ratio" should be substituted (277).

Coupling.—Kinesthetic connections of the visual cortex may account for an hemianopic patient "feeling" objects in the blind area [Nielson (278)]. Conversely, a defect in the motor cortex disturbs localization in a visual field area [Bender & Teuber (279)]. Harrington summarizes more diffuse (psychosomatic) coupling to the visual mechanisms and functions (280). The complete compensation in performance of aviators with low visual acuity affects the value of arbitrary visual tests [Viteles (281)].

Functions referred to central nervous system.—Experiment of Ades show that area 17 suffices for visual discrimination (282). The enhancement of border contrast by pentobarbital [Trent (283) would suggest a neural mechanism under strong inhibitory control. Similarly, reciprocal inhibition in rivalry is reduced by centrally depressant drugs [Bárány & Hallden (284)]. Objective fluctation and extinction on the cortex also correlate with visual perception [Bender & Teuber (285)]. Suppressor areas, shown to operate by sensory afferents and on sensory areas, may share in the homeostatic [Barker & Gellhorn (286)] or responsive control of visual activity.

Theory of integrating mechanisms.—Subjectively, form is invariant to changes of size and locus (241). Culbertson formulates the resulting requirements on pattern conduction between synaptic levels (287). The cortical representation of figures is probably temporal as well as spatial because α-activity scans the cortical thickness (Pitts & McCulloch (288)].

LITERATURE CITED

1. *Brit. J. Ophthalmol.* (Ophthalmic Literature), London (1947)
2. *Excerpta Medica*, Sect. XII (Ophthalmology), Amsterdam (1947)
3. *Ophthalmology in the War Years*, **I**, 1165 pp., 1940–43 (1946); **II**, 977 pp., 1944–46 (1948) (The Year Book Publishers, Inc., Chicago)
4. SORSBY, A., *Modern Trends in Ophthalmology*, 600 pp. (Paul B. Hoeber, Inc., London, 1947)
5. DETWILER, S. R., *Am. J. Ophthalmology*, **31**, 103–4 (1948)
6. *J. Optical Soc. Am.*, **32**, 40–41 (1942)
7. ROCHON-DUVIGNEAUD, A., *Les Yeux et la Vision des Vertebres*, 719 pp. (Masson et Cie., Paris, 1943)
8. NAGEOTTE, J., *Rev. gén. sci.*, **52**, 65–72 (1942)
9. VON SULLMAN, H., *Ophthalmologica*, **113**, 45–61, 108–28 (1947)
10. TAYLOR, W. O. G., *Ophthal. Lit.*, **2**, 3–18 (1948)
11. SYDENSTRICKER, V. P., HALL, W. K., BOWLES, L. L., AND SCHMIDT, H. L., JR., *J. Nutrition*, **34**, 481–90 (1947)
12. BAKKER, A., *Brit. J. Ophthalmol.*, **31**, 100–8 (1947)
13. OBRIG, T. E., *Arch. Ophthalmol.* (*Chicago*), **38**, 668–76 (1947)
14. HART, W. M., AND CHANDLER, B. F., *Federation Proc.*, **7**, 51 (1948)
15. HART, W. M., *Arch. Ophthalmol.* (*Chicago*), **37**, 692–93 (1947)
16. MAXWELL, L. J., MANKIN, J., REID, C. H., AND HARRELL, G. T., *J. Clin. Invest.*, **26**, 416–19 (1947)
17. MATTEUCCI, P., *Riv. Oftal.*, **2**, 153–73 (1947)
18. MATTEUCCI, P., *Rassegna ital. ottal.*, **15**, 484–98 (1946)
19. VIOLLIER, G., LABHART, H., AND SULLMAN, H., *Helv. Physiol. et Pharmacol. Acta.*, **5**, 10–12 (1947)
20. LABHART, H., SULLMAN, H., AND VIOLLIER, G., *Experientia*, **3**, 418–19 (1947)
21. CRISTINI, G., *Ophthalmologica*, **113**, 156–64 (1947)
22. FRADKIN, M. V., AND LEVINA, L. S., *Vestnik Oftalmol.*, **26**, 3–6 (1947)
23. SCHMERL, E., AND STEINBERG, B., *Am. J. Ophthalmology*, **31**, 155–58 (1948)
24. PANZARDI, D., *Boll. ocul.*, **26**, 570–80 (1947)
25. MAGITOT, A., *Ann. ocul.*, **180**, 1–9 (1947)
26. RADNOT, M., *Orvosok Lapja Népegészségügy*, **1**, 199–200 (1945)
27. SEDAN, J., *Rev. oto-neuro-oftal.*, **19**, 114–18 (1947)
28. BÁRÁNY, E., *Acta Ophthalmol.*, **25**, 189–93 (1947)
29. SONDERMANN, R., *Klin. Monatsbl. Augenheilk.*, **112**, 113–24 (1947)
30. HUBER, A., *Ophthalmologica*, **114**, 217–27 (1947)
31. PALM, E., *Acta Ophthalmol.*, **25**, 29–35 (1947)
32. DAVSON, H., AND DUKE-ELDER, W. S., *J. Physiol.* (*London*), **107**, 141–52 (1948)
33. HUPSEL, O., 112 pp. (Doctoral thesis, Utrecht Univ. 1947)
34. HUBER, A., *Ophthalmologica*, **114**, 228–41 (1947)
35. VANZETTI, G., AND SEIDENARI, R., *Rassegna ital. ottal.*, **16**, 65–77 (1947)
36. PALM, E., *Acta Ophthal.*, **25**, 139–64 (1947)
37. SCHOLZ, R. O., COWIE, D. B., AND WILDE, W. S., *Am. J. Ophthalmology*, **30**, 1513–16 (1947)
38. WILDE, W. S., SCHOLZ, R. O., AND COWIE, D. B., *Am. J. Opthhalmology*, **30**, 1516–26 (1947)

39. WANG, J.-C., *J. Gen. Physiol.*, **31**, 259–68 (1948)
40. KRAUSE, A. C., AND SIBLEY, J. A., *Arch. Ophthalmol. (Chicago)*, **36**, 328–48 (1946)
41. KINSEY, V. E., *Am. J. Ophthalmology*, **30**, 1262–66 (1947)
42. BÁRÁNY, E. H., *Acta Physiol. Scand.*, **13**, 95–102 (1947)
43. STOCKER, F. W., *Arch. Ophthalmol. (Chicago)*, **37**, 583–90 (1947)
44. DEVRIES, S., 92 pp. (Doctoral thesis, Univ. Amsterdam, 1947)
45. DAVSON, H., *Ophthal. Lit.*, **1**, 30 (1947)
46. BÁRÁNY, E., AND DAVSON, H., *Brit. J. Ophthalmol.*, **32**, 313–14 (1948)
47. DRUAULT, A., AND DRUAULT, S., *Ann. ocul.*, **179**, 531–39 (1946)
48. AJO, A., *Acta. Physiol. Scand.*, **13**, 130–49 (1947)
49. VILTER, V., *Compt. rend. soc. biol.*, **141**, 346–48 (1947)
50. O'DAY, K., *Nature*, **160**, 648, (1947)
51. GRANIT, R., *Nature*, **160**, 838 (1947)
52. HARTRIDGE, H., *J. Physiol. (London)*, **106**, 28–29 (1947)
53. EVANS, J. N., *Arch Ophthalmol. (Chicago)*, **37**, 182–88 (1947)
54. SMITH, G. M., SEITZ, C. F., AND CLARK, K. B., *J. Aviation Med.*, **17**, 590–95 (1946)
55. JAEGER, A., *Klin. Monatsbl. Augenheilk.*, **112**, 44–48 (1947)
56. DUGUET, J., DUMONT, P., AND BIALLIART, J. P., *J. Aviation Med.*, **18**, 516–20 (1947)
57. LOPRESTI, J. L., *Am. J. Ophthalmology*, **30**, 340 (1947)
58. VAIL, D., *Am. J. Ophthalmology*, **31**, 1–11 (1948)
59. BELL, P. G., AND O'NEILL, J. C., *Can. Med. Assoc.*, **56**, 475–81 (1947)
60. BEIN, H. J., *Helv. Physiol. et Pharmacol. Acta.* **5**, 190–201 (1947)
61. NAUTA, W. J. H., AND VAN STRAATEN, J. J., *J. Anat.*, **81**, 127–34 (1947)
62. TALBOT, S. A., *Federation Proc.*, **1**, 84 (1942)
63. SOLNITZKY, O., AND HARMON, P. J., *J. Comp. Neurol.*, **85**, 313–91 (1946)
64. COGAN, D. G., *Neurology of the Ocular Muscles*, 214 pp. (C. C Thomas, Springfield, Ill., 1948)
65. HOESSLY, G. F., *Helv. Physiol et Pharmacol. Acta*, **5**, 333–37 (1947)
66. CROSBY, E. C., AND HENDERSON, J. W., *J. Comp. Neurol*, **88**, 53–92 (1948)
67. SPERRY, R. W., *Anat. Record*, **97**, 293–315 (1947)
68. SCOBEE, R. G., *The Oculorotary Muscles*, 359 pp. (Mosby, St. Louis, Mo., 1947)
69. SCOBEE, R. G., *Quart. Rev. Ophthalmol.*, **4**, 1–18 (1948)
70. TSCHERMAK-SEYSENEGG, A. v., *Arch. Ophthalmol. (Graefe's) ver. Arch. Augenheilk.*, **148**, 101–6 (1947)
71. FRY, G. A., TRELEAVEN, C. L., WALSH, R., HIGGINS, E. L., AND RADDE. C. A., *Am. J. Optometry*, **24**, 329–34 (1947)
72. PACALIN, G., *Ann. ocul.*, **180**, 696–701 (1947)
73. KOOMEN, M. J., KNOLL, H. A., AND TOUSEY, R., *J. Optical Soc. Am.*, **37**, 527 (1947)
74. CORRADO, M., *Ann. ottal. clin. ocul.*, **1**, 171–82 (1947)
75. THOMSON, L. C., *J. Physiol. (London)*, **106**, 59–65 (1947)
76. WAGMAN, I. H., *Federation Proc.*, **7**, 128 (1948)
77. BÁRÁNY, E. H., AND HALLDEN, U., *J. Neurophysiol.*, **11**, 25–30 (1948)
78. KUNTZ, A., AND RICHINS, C. A., *J. Neurophysiol.*, **9**, 1–7 (1948)

79. WOLFF, E., *Trans. Ophthalmol. Soc., United Kingdom*, **65**, 164–69 (1945)
80. LAYTON, A., MORGAN, M. W., JR., AND OLMSTED, J. M. D., *Am. J. Physiol.*, **151**, 568–71 (1947)
81. MATTEUCCI, P., AND TOSELLI, C., *Rassegna ital. ottal.*, **16**, 407–17 (1947)
82. LOCASCIO, G., AND DELEONIBUS, D., *Boll. Ocul.*, **26**, 609–29 (1947)
83. O'BRIEN, J. M., AND BANNON, R. E., *Am. J. Ophthalmology*, **30**, 289–95 (1947)
84. BROZEK, J., SIMONSON, E., BUSHARD, W. J., AND PETERSON, J. H., *Am. J. Ophthalmology*, **31**, 191–98 (1948)
85. DUBOIS-POULSON, A., AND ROZAN, A., *Ann. ocul.*, **180**, 206–37 (1947)
86. WALD, G., AND GRIFFIN, D. R., *J. Optical Soc. Am.*, **37**, 321–36 (1947)
87. KATZ, J., *Klin. Monatsbl. Augenheilk.*, **111**, 219–23 (1946)
88. SCHOBER, H., *Arch. Ophthalmol. (Graefe's) ver. Arch. Augenheilk.*, **148**, 171–86 (1947)
89. CHAPANIS, A., *U. S. Dept. Comm. Pub. Bd. No. L60608* (1947)
90. IVANOFF, A., *J. Optical Soc. Am.*, **37**, 730 (1947)
91. KRATZ, J. D., *Am. J. Optometry*, **24**, 15–21 (1947)
92. HILDRETH, H. R., MEINBERG, W. H., MILDER, B., POST, L. T., AND SANDERS, T. E., *Am. J. Ophthalmology*, **30**, 1563–76 (1947)
93. HIRSCH, M. J., AND WEYMOUTH, F. W., *Am. J. Optometry*, **24**, 601–8 (1947)
94. DELLER, J. F. P., O'CONNER, A. D., AND SORSBY, A., *Proc. Roy. Soc. (London)* [B] **134**, 456–66 (1947)
95. JAEGER, A., *Arch. Ophthalmol. (Graefe's) ver Arch. Augenheilk.*, **148**, 152–61 (1947)
96. KOOMEN, M., SCOLNIK, R., AND TOUSEY, R., *J. Optical Soc. Am.*, **37**, 992 (1947)
97. PASCAL, J. I., *Arch. Ophthalmol. (Chicago)*, **37**, 83–84 (1947)
98. BIRO, I., *Ophthalmologica*, **115**, 156–66 (1948)
99. WEIDMANN, W., *Ophthalmologica*, **114**, 33–43 (1947)
100. HARTRIDGE, H., *J. Physiol. (London)*, **106**, 17P (1947)
101. FRY, G. A., *Optometric Weekly*, **37**, 1521–23 (1946)
102. LE GRAND, Y., AND GUILLEMOT, E., *Nature*, **159**, 132–33 (1947)
103. PFISTER, A., *Ophthalmologica*, **113**, 344–64 (1947)
104. GÁT, L., *Ophthalmologica*, **113**, 93–105 (1947)
105. WISKOVSKÝ, B., *Acta Oto-Laryngol.*, **35**, 367–76 (1947)
106. KOELLA, W., *Helv. Physiol. et Pharmacol. Acta*, **5**, 154–68 (1947)
107. HENDERSON, J. W., *Arch. Opthhalmol. (Chicago)*, **37**, 459–71 (1947)
108. COPAZZI, L., AND SALA, O., *Rev. oto-neuro-oftal.*, **22**, 50–65 (1947)
109. GÖTHLIN, G. F., *Acta Oto-Laryngol.*, **34**, 230–45 (1946)
110. WALD, G., *Federation Proc.*, **7**, 129 (1948)
111. BLISS, A. F., *J. Biol. Chem.*, **172**, 165–78 (1948)
112. BALL, S., COLLINS, F. D., MORTON, R. A., AND STUBBS, A. L., *Nature*, **161**, 424–26 (1948)
113. MORTON, R. A., SALAH, M. K., AND STUBBS, A. L., *Nature*, **159**, 744 (1947)
114. WALD, G., *Harvey Lectures, Ser.*, **41**, 117–60 (1946)
115. BLISS, A. F., *Federation Proc.*, **7**, 9 (1948)
116. WALD, G., *J. Gen. Physiol.*, **31**, 377–83 (1948)
117. ISHIMOTO, M., AND WALD, G., *Federation Proc.*, **5**, 50 (1946)

118. HARTLINE, H. K., AND MCDONALD, P. R., *J. Cellular Comp. Physiol.*, **30**, 225–53 (1947)
119. HARTLINE, H. K., AND MCDONALD, P. R., *U. S. Off. Naval Research Rept. No. JU 502* (1947)
120. MOON, P., AND SPENCER, D. E., *J. Optical Soc. Am.*, **35**, 43–65 (1943)
121. MACNICHOL, E. F., AND HARTLINE, H. K., *Federation Proc.*, **7**, 76 (1947)
122. FRY, G. A., AND ALPERN, M., *Am. J. Optometry*, **23**, 509–25 (1946)
123. HARTLINE, H. K., *Federation Proc.*, **7**, 51 (1947)
124. WULFF, V. J., AND JAHN, T. L., *J. Neurophysiol.*, **11**, 117–23 (1948)
125. LINDEMAN, V. F., *Am. J. Physiol.*, **148**, 40–44 (1947)
126. GERNANDT, B., *Acta Physiol. Scand.*, **15**, 88–92 (1948)
127. GRANIT, R., AND TANSLEY, K., *J. Physiol. (London,)* **107**, 54–66 (1948)
128. GERNANDT, B., AND GRANIT, R., *J. Neurophysiol.*, **10**, 295–301 (1947)
129. GRANIT, R., *J. Neurophysiol.*, **11**, 239–52 (1948)
130. GERNANDT, B., *Acta Physiol. Scand.*, **15**, 286–89 (1948)
131. GERNANDT, B., *J. Neurophysiol.*, **10**, 303–8 (1947)
132. GRANIT, R., *J. Neurophysiol.*, **11**, 253–60 (1948)
133. JUDD, D. B., *J. Optical Soc. Am.*, **33**, 294–307 (1943)
134. RIGGS, L. A., *Science*, **106**, 511 (1947)
135. MONNIER, M., AND BOSMA, F., *Helv. Physiol. et Pharmacol. Acta.*, **5**, 205–24 (1947)
136. CLARK, W. E. L., AND CHACKO, L., *Nature*, **160**, 123 (1947)
137. AUSTIN, G. M., LEWEY, F. H., AND GRANT, F. C., *Federation Proc.*, **7**, 4 (1948)
138. MONNIER, M., AND JEANNERET, R. L., *Ophthalmologica*, **113**, 1–11 (1947)
139. COHN, R., *J. Neurophysiol.*, **11**, 31–37 (1948)
140. COBB, S., *Arch. Neurol. Psychiat.*, **58**, 70–71 (1947)
141. CORRADO, M., *Ann. ottal., clin. ocul.*, **1**, 257–87 (1947)
142. BARNARD, R. D., *Ohio J. Sci.*, **47**, 132–33 (1947)
143. BARLOW, H. B., KOHN, H. I., AND WALSH, E. G., *Am. J. Physiol.*, **148**, 376–81 (1947)
144. SCHWARTZ, F., *Arch. ges. Physiol. (Pflügers)*, **249**, 76–86 (1947)
145. BARLOW, H. B., KOHN, H. I., AND WALSH, E. G., *Am. J. Physiol.*, **148**, 372–75 (1947)
146. ESTABAN, M., *Arch. Soc. oftal. hispano Am.*, **7**, 687–702 (1947)
147. FRANTZ, R., AND VOGEL, P. J., *Bull. Los Angeles Neurol. Soc.*, **11**, 135–44 (1946)
148. SCHOBER, H., *Graefe's Arch. Ophthalmol. (Graefe's) ver. Arch. Augenheilk.* **148**, 93–100 (1947)
149. STUDNITZ, G. v., *Klin. Monatsbl. Augenheilk.*, **111**, 154–73 (1947)
150. ROSE, H. W., AND SCHMIDT, I., *J. Aviation Med.*, **18**, 218–30 (1947)
151. SHEARD, C., *Federation Proc.*, **7**, 113 (1948)
152. SLOAN, L. L., *Am. J. Ophthalmol.*, **30**, 705–20 (1947)
153. UXOVA-KHYNOVA, A., *Časopis Lékařů Českych*, **86**, 336–39 (1947)
154. FEHILY, L., *Brit. Med. J.*, 220–222 (1947)
155. SHEARD, C., *J. Aviation Med.*, **17**, 526–32 (1946)
156. SLAUGHTER, D., *J. Lab. Clin. Med.*, **31**, 987–90 (1946)
157. DAVIS, S. N., *Federation Proc.*, **7**, 26 (1948)
158. CHAPANIS, A., *U. S. Dept. Comm., Pub. Bd. No. L60609* (1947)

159. GRIFFIN, D. R., HUBBARD, R., AND WALD, G., *J. Optical Soc. Am.*, **37**, 546–54 (1947)
160. PIRENNE, M. H., *J. Physiol.* (*London*), **106**, 25P (1947)
161. CRAWFORD, B. H., *Proc. Roy. Soc.* (*London*) [B]**134**, 283–302 (1947)
162. O'BRIEN, B., *J. Optical Soc. Am.*, **37**, 275–78 (1947)
163. PLATT, J. R., *J. Optical Soc. Am.*, **37**, 669–70 (1947)
164. FLAMANT, F., AND STILES, W. S., *J. Physiol.* (*London*), **107**, 187–202 (1948)
165. BROWN, R. H., *Am. J. Psychol.*, **60**, 254–59 (1947)
166. HAIG, C., AND HAIG, E. M., *Federation Proc.*, **7**, 47 (1948)
167. BAUMGARDT, E., *Compt. rend.*, **225**, 259–61 (1947)
168. IVANOFF, A., *Compt. rend.*, **224**, 1183–85 (1947)
169. WALLACH, H., *J. Exptl. Psychol.*, **38**, 310–24 (1948)
170. GALIFRET, Y., AND PIERON, H., *Année psychol.* (*Paris*), **42/43**, 231–48 (1947)
171. JALAVISTO, E., NIINI, R., AND REENPÄÄ, Y., *Acta Physiol. Scand.*, **12**, 147–70 (1946)
172. REENPÄÄ, Y., *Acta. Physiol. Scand.*, **15**, 26–37 (1948)
173. BRUMBERG, E. M., VAVILOV, S. I., AND SVERDLOV, Z. M., *J. Phys.* (*U. S. S. R*), **7**, 1–8 (1943)
174. HECHT, S., SCHLAER, S., AND PIRENNE, M. H., *J. Gen Physiol.*, **25**, 819–40 (1942)
175. VAN DER VELDEN, H. A., *Physica*, **11**, 179–89 (1944)
176. BOUMAN, M. A., AND VAN DER VELDEN, H. A., *J. Optical Soc. Am.*, **37**, 908–19 (1947)
177. BAUMGARDT, E. L. M., *J. Gen. Physiol.*, **31**, 269–90 (1948)
178. VAN DER VELDEN, H. A., *Ophthalmologica*, **111**, 321–31 (1946)
179. DEVRIES, H., *Nature*, **157**, 303 (1946)
180. TEN DOESSCHATE, J., *Ophthalmologica*, **112**, 1–18 (1946)
181. BOUMAN, M. A., AND VAN DER VELDEN, H. A., *J. Optical Soc. Am.*, **38**, 231–36 (1948)
182. ROSE, A., *J. Optical Soc. Am.*, **38**, 196–208 (1948)
183. BAUMGARDT, E. L. M., AND SEGAL, J., *Année psychol.* (*Paris*), **42/43**, 54–102 (1947)
184. REIMERT, L. J., *U. S. Dept. Comm., Pub. Bd. No. 51022* (1947)
185. HECHT, S., ROSS, S., AND MUELLER, C. G., *H. Optical Soc. Am.*, **37**, 500–7 (1947)
186. MARTIN, L. C., AND KANIOWSKI, W., *Nature*, **159**, 25–26 (1947)
187. HENDLEY, C. D., *J. Gen. Physiol.*, **31**, 433–55 (1948)
188. WALD, G., AND BURIAN, H. M., *Am. J. Ophthalmology*, **27**, 950–63 (1944)
189. RIESEN, A. H., *Science*, **106**, 107–8 (1947)
190. JONES, L. A., AND HIGGINS, G. C., *J. Optical Soc. Am.*, **37**, 217–63 (1947)
191. JONES, L. A., AND HIGGINS, G. C., *J. Optical Soc. Am.*, **38**, 398–405 (1948)
192. MISIAK, H., *J. Exptl. Psychol.*, **37**, 318–32 (1947)
193. ROUSSEL, F., AND WEEKERS, R., *Ophthalmologica*, **113**, 215–23 (1947)
194. TEUBER, H. L., AND BENDER, M. B., *Federation Proc.*, **7**, 124 (1948)
195. SLOAN, L. L., AND GILGER, A. P., *Am. J. Ophthalmology*, **30**, 1387–1405 (1947)
196. LAMAR, E. S., HECHT, S., SCHLAER, S., AND HENDLEY, C. D., *J. Optical Soc. Am.*, **37**, 531–45 (1947)
197. FRY, G. A., *J. Optical Soc. Am.*, **37**, 166–75 (1947)

198. IVANOFF, A., *Compt. rend.*, **224**, 1846–48 (1947)
199. WRIGHT, W. D., *Researches on Normal and Defective Colour Vision*, 383 pp. (Mosby, St. Louis, Mo., 1947)
200. CHUPRAKOV, A., *Vestnik Oftalmol.*, **17**, 680–86 (1940)
201. FRY, G. A., *Am. J. Optometry*, **25**, 162–79 (1948)
202. MAIONE, M., *Ann. ottal. clin. ocul.*, **72**, 467–90 (1940)
203. MANN, I., AND SHARPLEY, F., *J. Physiol. (London)*, **106**, 301–4 (1947)
204. MCCLURE, J. A., *Trans. Am. Acad. Ophthal. Otol.*, 671–74 (1947)
205. LOW, F. N., *Am. J. Physiol.*, **151**, 319–24 (1947)
206. SCOTT, J. W., AND SOLANDT, D. Y., *Rev. can. biol.*, **6**, 175 (1947)
207. MANDELBAUM, J., AND SLOAN, L. L., *Am. J. Ophthalmology*, **30**, 581–88 (1947)
208. GUGGENBÜHL, A., *Ophthalmologica*, **115**, 193–218 (1947)
209. GAUS, J., *Ophthalmologica*, **112**, 267–87 (1946)
210. PLICQUE, J., *Ann. ocul.*, **179**, 83–107 (1946)
211. LOW, F. N., *Am. J. Physiol.*, **148**, 124–33 (1947)
212. GORDON, D. A., *Am. J. Psychol.*, **60**, 202–25 (1947)
213. CLEMMESON, V., *Acta Physiol. Scand.*, **9**, Suppl. 27, 1–206 (1947)
214. HODEL-BOOS, M., *Ophthalmologica*, **115**, 25–46 (1948)
215. LIANG, T., AND PIERON, H., *Année psychol. (Paris)*, **42/43**, 1–53 (1947)
216. GRAYBIEL, A., CLARK, B., AND MACCORQUODALE, K., *J. Exptl. Psychol.*, **37**, 170–77 (1947)
217. CLARK, B., GRAYBIEL, A., AND MACCORQUODALE, K., *J. Exptl. Psychol.*, **38**, 298–309 (1948)
218. PATTERSON, L., JR., AND GRAYBIEL, A., *Federation Proc.*, **7**, 91 (1948)
219. GOLDMANN, H., *Ophthalmologica*, **114**, 147–58 (1947)
220. HARVARD UNIV., *U. S. Dept. Comm., Pub. Bd. No. L55807* (1947)
221. HARVARD UNIV., *U. S. Dept. Comm., Pub. Bd. Nos. 55801, 03, 04, 05, 10* (1947)
222. NAT'L. DEFENSE RES. COMM., *U. S. Dept. Comm., Pub. Bd. No. 51005* (1947)
223. HIRSCH, M. J., AND WEYMOUTH, F. W., *J. Aviation Med.*, **19**, 56–58 (1948)
224. JENKIN, L., *Brit. J. Physiol. Optics*, **6**, 1–23 (1947)
225. HARVARD UNIV., *U. S. Dept. Comm., Pub. Bd. No. L62428* (1947)
226. HARVARD UNIV., *U. S. Dept. Comm., Pub. Bd. No. L62427* (1947)
227. BROWN UNIV., *U. S. Dept. Comm., Pub. Bd. No. L45789* (1947)
228. SMITH, S., *J. Exptl. Psychol.*, **36**, 518–21 (1946)
229. CAMPBELL, D., *Brit. J. Ophthalmol.*, **31**, 321–35 (1947)
230. BURIAN, H. M., *Arch. Ophthalmol. (Chicago)*, **37**, 618–48 (1947)
231. BURIAN, H. M., *Am. J. Ophthalmology*, **30**, 1005–10 (1947)
232. BURIAN, H. M., *Arch. Ophthalmol. (Chicago)*, **37**, 336–68 (1947)
233. BURIAN, H. M., *Arch. Ophthalmol. (Chicago)*, **37**, 504–33 (1947)
234. MILES, P. W., *Am. J. Ophthalmology*, **30**, 885–96 (1947)
235. BRAUN-VALLON, S., AND HARTMAN, E., *Ann. ocul.*, **180**, 65–75 (1947)
236. KÖHLER, W., AND EMERY, D. A., *Am. J. Psychol.*, **60**, 159–201 (1947)
237. HARVARD UNIV., *U. S. Dept. Comm. Pub. Bd. No. L62429* (1947)
238. STEIN, A., *J. Optical Soc. Am.*, **37**, 944–62 (1947)
239. TEN DOESSCHATE, G., *Nederland. Tijdschr. Geneesk.*, **91**, 2841–52 (1947)

240. LUNEBERG, R. K., *Courant Anniversary Volume*, 215–40 (Interscience Publishers, Inc., New York, N. Y., 1948)
241. LUNEBERG, R. K., *Mathematical Theory of Binocular Vision*, 104 pp. (Princeton University Press, Princeton, N. J., 1947)
242. KARPLUS, S., AND WRIGHT, W. D., *Nature*, **160**, 647–48 (1947)
243. THOMPSON, L. C., AND WRIGHT, W. D., *J. Physiol. (London)*, **105**, 316–31 (1947)
244. HORNER, R. G., AND PURSLOW, E. T., *Nature*, **160**, 23–24 (1947)
245. THOMPSON, L. C., *J. Physiol. (London)*, **106**, 368–77 (1947)
246. HARTRIDGE, H., *Nature*, **160**, 831–32 (1947)
247. STILES, W. S., *Proc. Roy. Soc. (London)*, [B]**127**, 64 (1939)
248. HARTRIDGE, H., *J. Physiol. (London)*, 106, 9P (1947)
249. HARDY, L. H., RAND, G., AND RITTLER, M. C., *Arch. Ophthalmol. (Chicago)*, **38**, 442–49 (1947)
250. HARDY, L. H., RAND, G., AND RITTLER, M. C., *J. Gen. Psychol.*, **36**, 79–106 (1947)
251. BOSTRÖM, C. G., and KUGELBERG, I., *Ophthalmologica*, **114**, 95–99 (1947)
252. VOLK, D., AND FRY, G. A., *Am. J. Optometry*, **24**, 99–122 (1947)
253. GALLAGHER, J. R., LUDVIGH, E. J., MARTIN, S. F., AND GALLAGHER, C. D., *Arch. Ophthalmol. (Chicago)*, **37**, 572–82 (1947)
254. MCCORD, F., *J. Clin. Psychol.*, **3**, 197–98 (1947)
255. PICKFORD, R. W., *Nature*, **161**, 27 (1948)
256. PICKFORD, R. W., *Nature*, **161**, 687 (1947)
257. MALMO, R. B., AND GRETHER, W. F., *J. Comp. Physiol. Psychol.*, **40**, 143–47 (1947)
258. HECHT, S., AND HSIA, Y., *J. Gen Physiol.*, **31**, 141–52 (1947)
259. SZEKERES, G., *J. Optical Soc. Am.*, **38**, 350–63 (1948)
260. DEVRIES, H., *Ophthalmologica*, **113**, 224–26 (1947)
261. PRENTICE, W. C. H., *J. Exptl. Psychol.*, **38**, 284–88 (1948)
262. AHLENSTIEL, H., *Arch. Ophthalmol. ver. Arch. Augenheilk.*, **148**, 168–70 (1947)
263. WAGENAAR, J. W., *Ophthalmologica*, **113**, 227–29 (1947)
264. HELSON, H., AND GROVE, J., *J. Optical Soc. Am.*, **37**, 387–95 (1947)
265. HELSON, H., *Am. J. Psychol.*, **60**, 1–29 (1947)
266. MOON, P., AND SPENCER, D. E., *J. Optical Soc. Am.*, **33**, 260–77 (1943)
267. LUCKIESH, M., *J. Exptl. Psychol.*, **37**, 266–68 (1947)
268. BITTERMAN, M. E., *J. Exptl. Psychol.*, **37**, 269–70 (1947)
269. BITTERMAN, M. E., AND SOLOWAY, E., *Am. J. Psychol.*, **59**, 676–81
270. LAWSON, R. W., *Nature*, **161**, 154–56 (1948)
271. SIMONSON, E., BROZEK, J., AND KEYS, A., *Federation Proc.*, **6**, 184, 202 (1947)
272. CARMICHAEL, L., AND DEARBORN, W. F., *Reading and Visual Fatigue*, 483 pp. (H. Mifflin, Boston, Mass., 1948)
273. BARTLEY, S. H.. *Am. J. Optometry*, **24**, 372–84 (1947)
274. HOFFMAN, A. C., *J. Applied Psychol.*, **31**, 44–53 (1947)
275. SIMONSON, E., AND BROZEK, J., *J. Optical Soc. Am.*, **38**, 384–98 (1048)
276. MARTIN, L. C., AND PEARSE, R. W. B., *Brit. J. Ophthalmol.*, **31**, 129–44 (1947)
277. DARBY, W. G., AND CROUCH, C. L., *Illum. Eng.*, **41**, 565–69 (1946)

278. NIELSON, J. M., *Bull. Los Angeles Neurol. Soc.*, **12**, 195–96 (1947)
279. BENDER, M. B., AND TEUBER, L., *Arch. Neurol. Psychiat.*, **58**, 721–39 (1947)
280. HARRINGTON, D. O., *Trans. Am. Acad. Ophthalmol. Otol.*, 65–74, 78–89 (1947)
281. VITELES, M. S., *J. Aviation Med.*, **18**, 528–47 (1947)
282. ADES, H. W., *J. Neuropathol. Exptl. Neurol.*, **5**, 60–65 (1946)
283. TRENT, S. E., *J. Gen. Psychol.*, **36**, 65–78 (1947)
284. BÁRÁNY, E. H., AND HALLDEN, U., *Acta Physiol. Scand.*, **14**, 296–316 (1947)
285. BENDER, M. B., AND TEUBER, H. L., *Arch. Neurol. Psychiat.*, **55**, 627–58 (1946)
286. BARKER, S. H., AND GELLHORN, E., *J. Neurophysiol.*, **10**, 125–38 (1947)
287. CULBERTSON, J. T., *Bull. Math. Biophysics*, **10**, 31–39 (1948); **10**, 97–102 (1948)
288. PITTS, W., AND MCCULLOCH, W. S., *Bull. Math. Biophysics*, **9**, 127–47 (1947)

PHYSIOLOGICAL PSYCHOLOGY[1]

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A revision of Freeman's (1) textbook on *Physiological Psychology* has recently been published. The purpose, as represented, is to provide psychologists with a survey of pertinent physiological fact and theory and to give a systematic orientation to the study of psychophysiology. One hundred and forty-one pages are given to the description of receptor and effector mechanisms, 93 pages to an account of structure and function in the central nervous system, 116 pages to what is called integrative action of bodily mechanisms —including discussion of reflex action, theories of emotion, sensory fusion, cerebral dominance, and theories of facilitation and inhibition—and 167 pages to problems of motivation, sets and postures, learning, fatigue, and personality. There are few references to primary sources that are later than 1940.

Adrian's brief treatise (2) on *The Physical Background of Perception* will be of interest to psychologists. A description of the essential mechanisms of operation of the sense organs and of the motor and sensory areas of the brain, as measured by recording the electrical potentials accompanying nervous impulses, is presented in simple and relatively nontechnical language. Changes in the electrical activity of the brain during perception of a flickering light, shifting attention from visual to auditory stimuli, drowsiness, and an epileptic seizure are depicted and a brief theoretical discussion is given concerning the patterning of nerve cell activities relating to such psychological phenomena as stimulus equivalence, pattern discrimination, abstraction, generalization, and memory traces.

An elementary textbook on neurology, Gardner's *Fundamentals of Neurology* (3), will prove useful to students of physiological psychology. Clear and precise descriptions are given of the gross and microscopic neuroanatomy of the peripheral and central nervous systems, and neural pathology is related to clinical syndromes. The book is well illustrated by photographs and line drawings and could serve as a supplementary text for courses in physiological psychology.

[1] This review covers the period from January, 1947 to August, 1948.

The 1947 edition of *Howell's Textbook of Physiology* (4) will prove to be an invaluable aid to the advanced student of physiological psychology. The first 547 pages of this text are devoted to the physiology of the effectors, receptors, and peripheral and central nervous system. The chapters are authoritatively written in critical fashion by different contributors, and the documentation is adequate and up-to-date. The only limitation of this book for the psychologist is the relatively cursory treatment given to physiological mechanisms relating to language, conditioning and learning, and the complex intellectual processes.

It is the contention of Kantor (5) in *Problems of Physiological Psychology* that physiological psychology is a domain of equivocation and paradox and that the confused condition of the field calls for a new orientation with regard to its investigation and theory. Authentic physiological psychology is the specialized investigation of biological factors more or less closely integrated with the stimulus and response functions which, as essential psychological events, are inevitably set in organism-object interbehaviors as matrices. The contributions and misinterpretations of sensory physiopsychology, psychophysiology, experimental psychoneurology, clinical psychosurgery, psychochemistry, psychobiology, and psychosomatic medicine are interpreted as seen by Kantor. The book is profusely documented, but the cited experiments are not considered in terms of their technical excellence or inadequacy but, rather, in terms of the degree to which the derived conclusions differ from Kantor's position concerning authentic physiological psychology. Kantor is not concerned with the content of psychophysiological investigations but instead, with the relation between physiological psychology and psychology per se, and the logical interpretive significance of psychophysiological data.

Central Nervous System and Behavior

Additional evidence has been obtained recently in opposition to the earlier claims of Jacobsen that bilateral destruction of the frontal areas in the monkey destroys "immediate memory" as measured by delayed reaction techniques. Campbell & Harlow (6) tested six monkeys following bilateral destruction of the frontal lobes rostral to the premotor areas and compared their performances on a long series of delayed reaction tests with those of six normal monkeys. Although the operated animals in general

were inferior to control subjects, there appeared to be little question that the operation did not destroy "immediate memory." Two of the operated monkeys gave performances comparing favorably with those of the control animals, and one monkey solved 40-second delayed reactions. The results were obtained without recourse to any special condition of reward or illumination.

Additional evidence bearing on the same problem has been presented by Wade (7), who found that two monkeys with bilateral frontal lobectomies could respond successfully on 25-second delayed reaction tests following intraperitoneal injections of pentobarbital or dial, even though the dose was so large in one case that the monkey could no longer maintain an upright posture. This animal subsequently solved delayed reactions without sedatives. Wade concluded that the hyperactivity and distractibility of the operated undrugged monkeys had prevented their finding a solution to the problem, but that under sedation, they discovered and maintained the performance. Such an interpretation is in keeping with the fact that Harlow & Campbell utilized training procedures to minimize compulsive circling during the delay interval. Certainly these two experiments, in conjunction with findings presented earlier by Finan and Malmo, present evidence enough that destruction of the frontal areas does not destroy "immediate memory."

Evidence indicating that removal of the prefrontal lobes in monkeys may produce learning loss has been presented by Settlage, Zable & Harlow (8), who compared the behavior of five operated and five normal control monkeys on problems involving contradictory and antagonistic responses to similar and identical stimuli. No overlapping of learning scores was found between the groups, and the differences in performance were statistically significant. The differences, however, were of a quantitative, not qualitative, nature and the authors suggested that they resulted from the perseverative interference of reaction patterns which had been correct for one phase of the problem but had become incorrect subsequently.

Remarkable changes in the social behavior of macaque monkeys have been reported by Ward (9) following unilateral and bilateral destruction of the anterior third of the cingular gyrus, the anterior limbic area. After either unilateral or bilateral resection of this area (Brodmann's area 24), the monkeys lost their preoperative

shyness and fear of man and would approach the experimenter and examine his finger. No social responsiveness was shown to other monkeys either by grooming or by acts of affection. The operated monkey would walk and sit on its companions, take food from them, and exhibit surprise when they retaliated. Furthermore, this behavior did not lead to fighting, since the operated monkeys were never pugnacious or aggressive.

Van Waters & Sacks (10) present a Rorschach evaluation of the schizophrenic process following a prefrontal lobotomy. They point out that so-called "organic signs" are absent or secondary and that it is difficult by Rorschach examination alone to assess the disabling effects of the schizophrenia independently of effects induced by surgery, a conclusion in accord with a previous report by Kisker (11).

In a detailed study in which every effort was made to carry out all practical controls, Porteus & Peters (12) investigated the effect of psychosurgery on Porteus Maze Test performance. The scores of 55 lobotomized patients (17 rated as unimproved, 22 as improved, and 16 as much improved) were compared with scores of 55 matched criminals. A comparison of scores earned by patients on the initial (preoperative) test and the second (first postoperative) test showed a loss on the second test of 1.65 years of mental age. The control subjects showed a mean gain of 1.60 years on the second test, accountable doubtless to practice effects. This difference of 3.25 years is statistically significant and suggests, at the very least, temporary intellectual loss following lobotomy. The operated patients were still performing below their initial scores on the third test, and their performances on their fourth, fifth, and sixth tests were positively correlated with their rated postoperative adjustment. The authors point out that recovery from the operation is slow and that there is evidence of Porteus Maze loss which persists for over a year.

Freeman & Watts (13) have recently altered their previous intuitive-theoretical position concerning the nature of frontal lobe functions as revealed by psychosurgery. Foresight is no longer the exclusive function of the frontal areas. Instead, these tissues are concerned primarily with creative and artistic skills, next with social-recreational activities and occupational duties, and least with skills related to routine living. It would appear from their writings that psychoses have an unpleasant character-

istic of initially debilitating frontal areas and then gradually and progressively invading the more posterior cortical areas.

A comprehensive study of the effect of brain injury on human patients has been presented by Halstead (14). By factor analysis of a battery of 27 neuropsychological tests made on 50 recovered head injury cases, a battery of 13 tests was selected. Subsequently a final battery was formed of the ten tests which best discriminated subgroups in a criterion group of 23 patients. The subgroups consisted of psychoneurotics, traumatic head injury cases, and head injury cases with psychoneurosis. An impairment score of 0.1 was given for each test passed at or beyond a criterion score. The mean impairment score for a group of 45 cases consisting of both unilateral and bilateral frontal lobectomies was found to be six and three times that of normal controls and nonfrontal lobectomies, respectively. No correlation was found between the impairment index and computed area of the lesion, and no deficit was found to be occasioned by frontal lobotomy. On the basis of inconclusive data, it was deduced that patients convalescing from recent closed head injuries have impairment scores resembling those of patients with frontal lobectomies. The impairment revealed was independent of "psychometric intelligence," disturbances in language function, and sensory or motor defects. These studies led Halstead to conclude that "biological intelligence" is a basic brain function which is represented throughout the cerebral cortex but distributed in a gradient with maximal representation in the frontal areas.

The effect of unilateral decortication on conditioned responses in the cat has been described by Bromiley (15), who tested 12 normal and 12 hemidecorticate subjects. Training to the criterion of 22 conditioned responses in 25 trials, Bromily found that the normal cats learned more rapidly than the decorticate animals, but that there was considerable overlapping between the two groups. The operation did influence markedly the form of the response, since the conditioned response in the normal cats was typically flexion of the shocked leg, whereas the conditioned response tended to be flexion of the unshocked leg in those subjects in which the unconditioned stimulus was applied contralateral to the excised cortex.

Moss & Harlow (16) have pointed out that sophisticated and test-wise monkeys may still show a remarkably high level of performance on delayed reactions, discrimination problems, and dis-

crimination reversal problems after extensive unilateral decortication combined with prefrontal lobotomy. These data suggest that extensive preoperative training may obscure any obvious effects of marked cortical damage.

Bromiley (17) has reported conditioning of responses in a dog after removal of the neocortex. This animal survived for 33 months and the histological check subsequently made revealed that only fragments of neocortex remained. Using a conditioned stimulus of sound and an unconditioned stimulus of weak electric shock, Bromiley was able to get precise, differentiated conditioned responses in less than 700 training trials. At the end of this period the conditioned response to sound was extinguished and a conditioned response to light formed. This procedure is described as giving "a discriminated conditioned response." It should be pointed out that Bromiley's dog never developed a completely stable conditioned response that would appear without fail throughout a test period and that the conditioned responses obtained were easily forgotten and very readily extinguished experimentally. Furthermore, although the author speaks of discriminated conditioned responses, discrimination between stimuli within a single sensory modality was not demonstrated.

An amazing degree of sparing of motor coordinative functions following multiple transections of the motor and sensorimotor cortex has been reported by Sperry (18). Multiple linear incisions were made through the surface of the cortex in nine macaque and two spider monkeys, and the depth of the incisions, which either passed through the cortex or into the sixth layer, was checked by histological examination. Even though the electrostimulable points in the cortex for movement of the shoulder, elbow, wrists, and digits had been separated from each other by the incisions, there was no incoordination of hand and arm movements and only transient weakness in fine, discriminative, manipulative finger movements. One week after the operation, uninstructed observers could not, even with close study, determine which was the affected arm. Similar results were obtained when linear incisions were placed on both sensorimotor cortices. Actual excision of the same areas, carried out as a control procedure, gave rise to severe paralysis of the arm and hand contralateral to the lesion, and this paralysis persisted with only slow improvement, for a month or longer.

Equally surprising results were reported by Smith (19), who

administered a large battery of sensorimotor and verbal reaction time tests to six patients before and after they underwent complete or nearly complete section of the corpus callosum. Significant loss was found in measures of simple reaction time, but not in the presumably more complex functions of discriminative reactions and verbal associations. Careful tests demonstrated that sensorimotor responses involving presumed uncrossed and crossed hemispheric relations were not differentially affected by the sectioning of the two sides of the cerebral cortex. These data indicate that it is unlikely that the bilateral neural relations deemed basic for the crossed responses are determined by impulse channels at the cortical level through the intercortical neurones forming the commissural pathways.

The problem of central nervous reorganization after nerve regeneration and muscle transposition has been critically reviewed by Sperry (20), who has organized, summarized, and interrelated the data from more than 300 investigations.

Experimental tests on the recovery of eye movements by 23 mid- and late-larval tadpoles following section of the oculomotor nerve and intracranial excision of the trochlear nerve were made by Sperry (21). Persistent wheel movements in the caudal direction accompanied by some medial deviation were obtained, and this behavior was taken to indicate that misregenerated fibers had retained their original central reflex timing without adjustment to the new motor terminations. In 12 frogs the roof of the orbit was opened and the individual nerve branches to each of the six main ocular muscles were divided. Following nerve regeneration complete recovery was obtained in seven animals and good recovery in the others, indicating that the loss previously reported following oculomotor nerve section was truly attributable to fiber misdirection. Cross union between the central end of the divided trochlear nerve and the peripheral end of the divided oculomotor nerve resulted in wheel movements in the reverse direction from normal, giving additional evidence that oculomotor nerve fibers can establish functional connections with foreign muscles without undergoing adaptive readjustment in their central reflex relations. Recovery of normal motor functions did occur, however, following transection of the oculomotor nerve in very early larval stages in tadpoles.

Having previously shown that no adaptive functional adjust-

ments took place after connections from spinal centers to antagonistic limb muscles had been exchanged in the rat, Sperry (22) subsequently investigated the effect in the monkey of crossing branches of the primary flexor and extensor muscles of the elbow. Thus the nerves were forced to regenerate into muscles antagonistic to those which they had formerly supplied. Four spider monkeys and two macaques served as subjects. In detailed tests, use of the experimental arm without contracting the test muscles was ruled out by measuring the monkeys' responses to food when the animals were forced to reach through a tube which extended from the shoulder to near the elbow. Reversed movements appeared during the early stages following nerve regeneration and persisted in some cases for months and even years. Differences, however, in the behavior of the monkey and the rat were marked. In the rat, the responses were carried out with full intensity and scope as though the animals were insensible of the reversal, whereas in the monkey, the appearance of reversal usually caused a break in general activity at the moment, with a turning of attention to the arm and repeated attempts to improve arm movement. Direct inhibition of reversal movements was the first sign of recovery in the monkey. Positive readjustment in the active contractions of the muscles supplied by the crossed nerves was achieved to some degree by all animals, but learned performances frequently showed little or no transfer to new situations. Three-fourths anesthetic dosages of pentothal gave variable results. There was a rapid recovery from temporary deficit produced by removal of the frontal areas. Four monkeys sacrificed at the end of the experiment were subjected to careful anatomical checks, and the brachial nerves were dissected free and stimulated electrically to test for the presence of nerve fibers innervating their original muscles.

Transplantation of the right eye from donor animals into the left orbit of new hosts and subsequent excision of the contralateral eye was accomplished in embryo frogs by Sperry (23). No animal was subsequently used if there was any indication that vision had been re-established, and all animals used were subjected to post mortem check to insure that the optic nerve had not regenerated. The timing of the operations was such that seven amphibians had never experienced vision and nine had experienced vision only through the subsequently excised eye. Two animals in the former group and three in the latter showed good and properly directed

reactions, evoked through labyrinthine stimuli, to rotation in both vertical planes of the body. Defects in intensity of response and qualitative abnormalities in the direction of response were related to incomplete postoperative recovery of the extraocular musculature, or to displacement of the dorsoventral or the nasotemporal axes. The experiments show that the reflex associations of the vestibulo-ocular system in the frog are not patterned by training but are laid down directly in growth in a predetermined manner. The obtained movements in the most successful cases were similar to those found in control subjects in which the optic nerves had not been severed until the time of testing, and in the other cases the nature of the consistently misdirected reactions correlated with disorientation of the eyeball and alteration of the insertion of the muscles.

Evidence that the functional relations between retina and visual centers are strictly and systematically predetermined by growth-regulating factors irrespective of functional adaptation is presented by Sperry (24), who effected reciprocal end-to-end crossing of the optic nerve in 21 anuran amphibians and contralateral transplantation of the eye in two anuran and 12 urodele amphibians. Crossing the optic nerves gave reversed optokinetic responses. Errors of localization, as tested with a housefly impaled on a fine wire, were quantitatively related in an inverse manner to the distance of the stimuli from the midsagittal plane. There was no evidence of inhibition or of adjustment to errors of either of these two kinds. Following transplantation of the eyes, the nature of the errors as measured both by optokinetic responses and tests of spatial localization was appropriately related to whether the dorsoventral axis or the nasotemporal axis of the eye had been inverted. No sign of correction or even inhibition of the maladaptive reactions was noted in any of these animals.

The importance of the problem of the relation between structural variation and behavior has been emphasized by Lashley (25). In a significant paper he has pointed out the existence of wide interspecies and intraspecies differences in the structure of the nervous system and indicated the great need, in spite of inherent difficulties, for genetic studies of such neurostructural variations in relation to behavioral variations. The article is replete with interesting examples of discovered variability, including comparison of brain weight of rodents and cetacea, familial resemblances in

cortical fissuration pattern in man, individual variation in myeloarchitectural pattern of the thalamus, and wide range in cell count per unit volume from identical areas of the brains of a series of spider monkeys.

Of considerable interest to physiological psychologists are the recent theoretical developments in neurophysiology which exploit the concept of the "reverberating circuit." The important demonstration of the interdependence of the cerebral cortex and thalamus which provides the circuits most prominent in subsequent theorizing was made by Dusser de Barenne & McCulloch (26). In this experiment, performed on monkeys under dial anesthesia, it was shown that as long as a given cortical area was connected with the related thalamic nucleus, "normal" cortical and thalamic rhythms were present. When the cortex was separated from the thalamus, these rhythms vanished. One animal was kept for two and a half years after cortical undercutting, and at the end of that time still showed abnormal activity from those areas (parts of arm and leg area 4) which had been undercut, but normal activity from other cortical areas.

The formal demonstration has been made that, if an animal possesses reverberating circuits, it may respond to universals rather than to mere specifics, since the reverberating circuits persist in time and are not confined to the instant of their original activation. This concept, with some derivatives, has been developed by McCulloch (27) and McCulloch & Pitts (28). Combined with the conception of the organism as a feed-back or servo-mechanism advanced by Rosenblueth, Wiener & Bigelow (29), this development makes possible a theoretical frontal attack on many problems besetting the theoretical psychologists. When the concept of reverberating circuits is extended to cover circuits which are completed outside the central nervous system, as has been done in the above articles, it is possible to place in the general theoretical system of reverberating circuits some which go through the musculature (the proprioceptive "backlash"), and even some which go outside the organism itself, as may be exemplified by the action of the corpora quadrigemina in centering the eyes on a stimulus (30).

An interesting special extension of the general theorizing is the formal derivation of visual and auditory "figure" functions (31). Combining previous conceptions with the concept of "scanning"

processes in the cortex led the authors to suggest a mechanism by which the organism might respond to chords rather than to specific tones, or shapes rather than to specific visual stimulation.

It should be remembered that the demonstrations are on a formal level and not rigidly supported by appropriate experimental evidence at all steps. For the present it may be best to recognize the importance of reverberating circuits for the understanding of relatively short-term persistence in behavior, as was pointed out by Jones (32), but reserve judgment on extensions of the theory, and especially to recognize the possibility that long-term sets and memories may actually require structural or persistent biochemical change within the nervous system.

Electroconvulsive Shock

Since the use of electroconvulsive shock therapy has become so widespread in the treatment of human neurotic and psychotic patients in spite of limited knowledge of its effects on psychological functions, it is not surprising that a number of psychological studies attacking this fundamental problem have been recently carried out.

A preliminary study was reported by Stone (33) on the effects of electroconvulsive shocks on the daily activity of albino rats as measured by the use of Slonaker-type revolving drums. Six adult female rats served as subjects and their activity was recorded for three control weeks and then for three alternating five-day periods of shock and no-shock, plus two additional no-shock periods. The results clearly show that the electroconvulsive shocks greatly reduced the amount of activity for a short period of time. The major change appeared within 24 hours of shock initiation and disappeared within 48 hours after the last convulsive shock was administered. Within a two-week period after the last convulsion the majority of animals closely approximated their preshock levels of daily activity.

Duncan (34) compared maze behavior in a group of 20 rats subjected to electroconvulsive shock, and 10 control animals. The subjects were trained for 45 trials to turn left on a single-unit elevated T-maze, following which they were lured by means of a much larger food reward to turn right for from four to seven trials. Electroshock was then introduced. The shocked animals showed a greater tendency than the control rats to return to the old, left-

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going habit, the difference being significant at the 5 per cent level of confidence. The author concluded that this indicated an amnesia or disorganization of the recent habit which allowed the older imcompatible habit to regain dominance.

The effect of electroconvulsive shock upon the performance of a previously learned problem was investigated by McGinnies (35). Twenty albino rats (five of which succumbed late in the experiment following convulsions) were trained to a rigorous learning criterion on a Stone-type 14-unit elevated maze. Postlearning shock testing was then carried out daily for 23 days, with maze practice coming four hours after a convulsive incident. No increase in errors was found during this period, but there was a marked increase in running time, with great individual variations in this regard. When practice was carried out for seven additional days during which no convulsions were induced, the running time progressively decreased until preshock time was approximated.

The influence of a series of 10 daily electroconvulsive shocks on subsequent maze learning by young rats was measured by Eriksen, Porter & Stone (36). Groups of 56 and 66 rats were trained on the Stone multiple T-maze, 10 days and 20 days following a series of 10 convulsive shocks given at the rate of one a day. The shock series was initiated when the rats were 20 and 21 days of age. In both experiments the differences between the shocked animals and their controls in total forward-going errors were highly significant, although no significant differences were obtained between the two experimental groups. Recovery from the effects of electroconvulsive shocks seemed to be as complete after 10 days as after 20 days. No gross behavioral differences between the experimental and control groups were noted either before or during the maze trials.

The effect of grand mal and petit mal seizures induced in rats following each day's training in a three-choice-point T alley maze was measured by Hayes (37). Grand mal seizures were induced in a total of 48 animals which were placed in a separate shocking apparatus more than an hour after removal from the maze goal-box, and similar seizures were induced in 20 rats by administering shock in the goal box 30 seconds after arrival there. These subjects comprised the grand mal "confusion" and "affect" groups, respectively. Petit mal seizures were induced in two additional groups of rats, an unspecified number of animals being given the

"confusion treatment" and 20, the "affect" treatment. Two control groups of ten rats each were also trained but never given shock. Significant differences were obtained between the grand mal confusion group and the control groups both in median running time and mean error scores. The time and error learning curves for the petit mal confusion group lay between the learning curves for the grand mal confusion rats and the control subjects, but the data are interpreted cautiously because of failure to produce petit mal seizures consistently. Where seizures were produced in the goal box, the rats demonstrated emotional effects including defecation, failure to go to the goal, and lack of interest in the reward. It was concluded that the rats "very definitely dislike convulsive shocks" and that the treatment tends to cause them to respond to a threatening situation by passive submission. Summarizing the entire study, the author concluded that the shocked rats' poor maze performance was actually due to a loss of cognitive function, since there was little evidence to support any alternative hypothesis.

Porter & Stone (38) compared maze performance in 10 etherized rats and 13 nonetherized rats administered a series of equivalent electroshocks. The animals were given one trial per day for 26 days on a seven-unit Warden Multiple-U maze before being subjected to a daily shock for 10 days and a maze trial approximately 23 hr. after each shock treatment. Following the electroshock series the subjects had daily single maze trials for 21 days, then a 40-day period without training, and finally, 10 additional maze trials given one per day. The shocks produced grand mal attacks in the nonetherized rats, but only a single initial contraction in the ether group, or, in a few cases, an additional slight flutter. Time scores were greatly increased for the nonetherized animals during the shock period and the 10 days immediately following, whereas the etherized animals showed neither improvement nor loss as measured by running time. The difference between the two groups was highly significant as measured by Alexander's method of trend analysis. These data are in keeping with those reported by McGinnies. Unlike McGinnies, however, Porter & Stone found evidence for increased total error scores in the 30-day shock-recovery period for the convulsive rats as compared with the etherized subjects, although no separate five-day period gave significant results. There were no differences between the two groups during

the final relearning period. In a second experiment reported in the same article, a series of 10 electroconvulsive shocks was given to 15 etherized and 15 nonetherized rats following less complete learning of a more complex maze. The subjects had a daily trial for 15 days on a 12-unit multiple T-maze, 10 shock treatments followed by maze trials, and 15 postshock trials. The authors report even greater differences in performance between the two groups than in the earlier experiment. Again they found that although time scores were more seriously affected than error scores, the differences in error scores were statistically significant. Differences between the etherized and nonetherized groups were not maintained throughout the 15-day postshock testing period.

That impairment of maze-learning by rats is not the only learning performance to suffer as a result of electroconvulsive shock was demonstrated by Horowitz & Stone (39). These investigators used the Stone serial light-discrimination apparatus to compare groups of 10 control and 13 experimental animals on the formation and subsequent reversal of a habit. After 40 days of single training trials, the experimental animals were subjected to 15 shocks, one shock per day about two hours after testing. Both the experimental and control groups were then run for 10 days with clips on their ears but were not given shocks. Finally, both the experimental and control animals were trained on the interference habit to a criterion of four out of five perfect runs. During the shock period the experimental animals made significantly more errors than the normal control animals, and this held true for any five-day period of shock. During the 10 postshock days, the experimental group improved and their performance approached, without quite reaching, their former level or the level of the control group. Although the performance of the shock-group rats was superior to that of the controls early in training on the interference problem (since they had learned the previous problem less completely), they required a significantly greater number of trials to reach the criterion.

A high degree of consistency is found in all these studies on the effect of electroconvulsive shock on the learning performances of albino rats. Electroconvulsive shock produces decreased efficiency on standardized learning measures, and the differences persist for a time after the shock periods cease. No permanent, or even long-persisting, disabilities have been demonstrated. Time

measures of performance appear to be particularly vulnerable, although increased error scores also accrue, particularly during the period that the electric shocks are actually being given.

Stone (40) tested 15 psychiatric patients on the Army Alpha Test both during and after the course of electroconvulsive shock treatment. Five forms of the test were administered and, in so far as possible, at the following times: one day after the first convulsion, one day after the ninth or tenth treatment, and one day, one week, and three weeks after the final treatment (usually the twentieth). The trend of the mean test scores was downward during the course of shocks, with a maximum average loss of about 20 points. During the postshock period, the trend of scores was upward, with the final test scores being about 15 points above the initial test scores. Limited data from high school and college entrance tests on these patients suggest that the preillness level of test ability was probably regained within a month after treatment ended.

A detailed study of the influence of electroshock therapy upon memory has been described by Zubin (41). Lists of meaningful and semimeaningful words were presented on cards and learned as paired associates. Retention was measured by recall, recognition, and relearning. Removing the influence of the original learning scores from the relearning scores by analysis of covariance revealed that the savings during the shock period vanished completely. Thus there was every indication that retention was completely eliminated by shock. This was interpreted as meaning that the memory traces were disorganized rather than destroyed. Recall memory was also abolished by shock. The objectively measured loss on recognition tests was slight, the differences between the control and treatment tests not being statistically significant. In spite of the patients' ability to respond with reasonable adequacy on the objective recognition tests, they typically protested when the recognition cards were shown to them after shock that they had never seen these cards before. Zubin points out that this "apparent loss of familiarity" is not limited to the described experimental situation, but also extends to loss of familiarity for objects and events personal to the tested subject, and the author suggests that this phenomenon may play an important role in the therapeutic process associated with electroconvulsive shock.

Abnormal Seizures

The conditions influencing the production of abnormal ("audiogenic") seizures in the rat have been investigated in a series of recent studies by psychologists. The effect of repeated stimulation upon the frequency and nature of these seizure patterns has been studied by Maier, Feldman & Longhurst (42). These investigators subjected one group of 20 rats to daily two-minute key-jingling tests for 135 days, and a second group of 20 rats to weekly two-minute tests for 19 weeks. Ninety per cent of the susceptible rats developed seizures within seven test periods. Daily, but not weekly, testing produced a reduction in the frequency of seizures. The decrease was primarily in the milder types of seizures, the abortive running seizures, and the running seizures without convulsions.

Maier & Longhurst (43) present evidence favorable to a previously advanced hypothesis that conflict is a factor in the production of audiogenic seizures. Eighty-one rats from 18 different strains were used as subjects, with 37 of these animals forming the experimental group and 44 the control group. The experimental rats were trained in a Lashley jumping box to respond positively to a small black circle on a white background and negatively to a small black circle on a white background. Training continued until the animals reached the criterion of 10 errorless trials on each of three successive days. They were then taken from this double window training situation and confronted with a single window test situation, with the single positive or negative training card presented in irregular order 10 trials a day for 2 four-day periods. Failure to jump was followed in 30 sec. by an air blast. This seizure testing was carried out for 2 four-day periods separated by a seven-day rest interval. The control animals were tested only in the single window situation with all conditions the same as those for the experimental rats save for the fact that the negative card was followed 30 sec. later by an air blast of 35 sec. duration, and the positive card by a five-second air blast. Careful tests showed that the conflict rats received less exposure to air blast per trial than the control animals. The mean frequency of seizures for the experimental group was 1.6, and for the control group 0.44, a difference significant at the 1 per cent confidence level. Thirty-eight per cent of the experimental subjects and only 9 per cent of the control animals had seizures. The

authors attribute the differences between the two groups to the introduction of conflict, since the essential difference in treatment of the two groups lay in the fact that the positive and negative cards had significance for the experimental group and had no significance for the control group.

Any assumption that conflict per se precipitates convulsive seizures was questioned by Lazovik & Patton (44), who trained rats on a Lashley jumping box with an electrified grid and then tested one group of 10 rats on the one-window conflict apparatus, and another group of 12 rats on the two-window conflict apparatus. The experimental animals were placed on a magnesium-deficient diet and tested 10 trials daily for a three-week period. Seventeen of 18 magnesium-deficient rats became susceptible to seizures, which showed increasing severity with increasing magnesium deficiency. The experimenters found no evidence, however, that convulsive seizures were associated with forced reactions in the conflict situation alone, and they state that any "conflict" situation which utilizes hunger motivation by reduction of food intake must be carefully controlled to prevent lowering of the seizure threshold through nutritional deficiencies alone.

The two previously cited experiments are by no means alike and not of necessity contradictory. Lazovik & Patton find that conflict adds no measurable increment to seizure frequency in a situation under conditions of internal state that make a rat highly seizure-prone. Maier & Longhurst find that conflict may be a factor in the production of seizure frequency in a situation in which seizure frequency is otherwise relatively low. In the situation chosen for study less than 10 per cent of the nonconflict rats developed seizures, whereas the same authors had found that key jingling without conflict would produce seizures in 75 per cent of rats presumably from the same stock. Such data suggest that "conflict" may be shown to be a factor in the frequency of elicitation of seizure responses whether or not it may be of enough importance to give significant insight into psychopathological processes.

Patton (45) has presented further evidence that dietary factors are important in the frequency of sound-induced seizures in an experiment in which a total of 462 rats from 80 different litters were maintained under seven different dietary conditions and subjected to standardized seizure testing employing a resonating buzzer

stimulus. Tests began when the rats were 21 days old and were carried out initially every other day for 10 days, then every fifth day for 25 days. The per cent of seizures ranged from 8.3 to 67.4. High per cents of seizures were obtained when the rats were maintained throughout the experiment on a basal diet or on Purina Chow. Good protection from sound-induced seizures was obtained by supplementing the basal diet with either five additional vitamins, rice polish concentrate, or ventriculin. An intermediate degree of protection was given by supplying liver concentrate or brewers' yeast. The addition of vitamins and vitamin concentrates did not dramatically reduce seizure frequency in the affected animals in this study, in contrast to the remarkable improvement shown in rats with magnesium deficiency when magnesium supplements were given.

Continuing his analysis of factors influencing sound-induced seizures, Patton (46) observed a high degree of association between suppurative middle-ear disease and susceptibility to sound-induced seizures in groups of young albino rats. On the other hand, mature rats that had had labyrinthitis might still show a low incidence of sound-induced seizures.

Patton (47) has demonstrated that the hamster, as well as the rat, is susceptible to sound-induced seizures under conditions of magnesium deficiency. Twenty-two hamsters maintained either on an adequate diet or given supplemental intraperitoneal magnesium injections failed to show seizures, whereas 26 hamsters on a magnesium-free diet died as a result of seizures unless quickly placed on adequate magnesium diet.

Motivation

The nature of the diurnal course of water and food intake in rats about 180 days of age was sketched by Siegel & Stuckey (48). Measures were made on 16 subjects four times daily for three successive days. Maximum food and water intake was statistically significantly greater at the night hours than during the day. The experimenters point out that this relates well to the activity cycle of the rat and probably represents a cycle "set" by the animal, since the subjects had been maintained on ad libitum drinking and feeding since weaning.

The relationship between number of hours of water deprivation

and voluntary water intake in a five-minute period was determined by Siegel (49) on four groups of 15 albino rats deprived of water for 6, 12, 24, and 48 hours, respectively. Water intake was measured using Richter-type calibrated drinking tubes. Temperature was thermostatically regulated between 76 and 78 degrees, and the animals were individually housed. The relationship between water intake and privation interval represented graphically was found to be slightly sigmoid. No data on the significance of the differences between the points are given. Body weight loss was also measured and, when related to hours of water privation, gave a negatively accelerated curve.

Bindra (50) has devised an ingenious method for studying water hoarding in rats, using dentists' cotton rolls soaked in water to form transportable water pellets. Comparison of food and water hoarding was made on 12 rats, with the order of drive condition presentation balanced. Both food and water series began with five deprivation days, followed by five test days under continued deprivation, and concluded with five test days under drive satiation. The rats were classified as "hoarders" and "non-hoarders" according to meeting or failing to meet the criterion of transporting at least seven pellets per test in at least three of the five tests given during deprivation. Since the selection of the subjects was made on the basis of data derived from the experiment per se, the important variables were hopelessly confounded. The "hoarders" gave similar mean hoarding scores for both food and water pellets. The curves show a steep initial rise and then decline during the deprivation test periods, and continued slow decline which does not reach zero during the satiation test periods. Bindra points out that the persistence of water hoarding on the satiation days cannot be explained on the basis of failure to recover from prolonged effects of previous deprivation, since water ingested after deprivation is completely absorbed within an hour. This would have been an interesting finding if the experimental variables had been kept discrete, if a control group never subjected to deprivation had been run, and if the significance of the differences had been statistically determined. In a second experiment three consistent "hoarders" were selected from the original 12, and these animals hoarded water primarily when they were water-deprived, and food when they were food-deprived. It should be noted, however, that

the three rats consistently hoarded a considerable number of food pellets on water deprivation days. Rather than postulate multiple instincts to hoard multiple incentives, Bindra suggests a drive to transport materials to the "home," with the type of material transported being influenced by multiple internal and external stimuli.

Further analysis of the hoarding response in rats was made by Bindra (51) in an experiment in which eight rats with water and Purina pellets always available were allowed to hoard either bottle caps filled with wet mash or Purina pellets. A marked preference for the bottle caps with wet mash was demonstrated, suggesting that a deficiency of certain substances in the body is not a necessary condition for the hoarding of food and that palatability may be an important factor in the release of the food hoarding response.

Hunt and associates (52) make a joint report of three experiments (all differing slightly) designed as a recheck of the earlier finding of the senior author that infantile-feeding frustration exerts a subsequent effect on adult food hoarding. A total of 32 experimental and 31 control subjects were used, the control rats being fed regularly, and the experimental rats irregularly for 15 days after weaning. Ninety-one to 190 days after the original infantile-feeding frustration the two groups were compared for hoarding scores obtained in 30-minute tests on four consecutive days. No single one of the repetition studies gave statistically significant results, but the combined data of the three separate experiments and the one of the two earlier researches which had given statistically significant results gave, as might be expected, statistically significant differences. Since the experiments were not identical, such procedures were obviously unjustified. The authors scrupulously present all pertinent data and are aware that other factors than the tested independent variable may be operating. They point out that the weight differentials between the experimental and control rats had not disappeared in the second or third experimental repetitions (in which the bulk of the differences occurred) when the hoarding tests were conducted. They indicate the generality of their disputable discovery by reference to two reports from *Time* magazine.

A review of experimental material bearing on the problem of hoarding in rats has been presented by Morgan (53). The influence of experience, emotional adaptation, temperature, food-deprivation, bodily metabolism, infant-deprivation, constitutional fac-

tors, frustration, home conditions, visual stimulation, and social competition are described.

Young (54) carried out an experiment on the influence of food preferences on running rate and on learning, using 39 rats as subjects and using both single and double food incentive situations. Preference tests were run on sugar, wheat, and casein and a uniform and stable preferential series was established which showed slight difference between sugar and wheat and marked differences between both of these and casein. Rate of running in the apparatus and increase in rate of running during testing were directly and positively related to the palatability of the test foods as determined by the preference tests. Since, however, the rate of improvement with practice (learning) was approximately constant for each of the three incentives when total running time was equated, Young suggests that the results fail to support the law of effect as a law of learning. It would seem that little importance could be attached to this negative finding, since an experimental situation in which an incentive is presented in the middle of a trial is not likely to be a delicate and precise device for measuring the influence of incentives on learning.

Failure of rats to self-select an adequate diet when allowed free choice of purified dietary components has been reported by Pilgrim & Patton (55). The growth rate of 14 control rats maintained on a basal diet was compared with that of 96 experimental animals allowed ad libitum choice of the four dietary components of the basal diet—casein, salts, sucrose, and fat. Appropriate supplementary vitamins were also given. Each of the dietary components was presented in a specially designed cup to minimize spilling, and the position of the cups was changed in a predetermined irregular order to prevent habitualized patterns of choice. About a third of the rats on the free choice diet gained at a subnormal rate as a result of an inadequate consumption of casein, indicating that nutritional or physiological need is not always effectively related to appetite. The stunted animals were adequately self-supplied for salts and calories.

Adolph (56) has reported that albino rats given diets mixed with kaolin, cellulose, or water increased the quantities of material, but not the quantities of nutrients ingested, over those taken under control conditions. Limited food or water privation decreased the consumption of the unlimited item. Recovery from the reduc-

tion of body weight resulting from complete food or water privation for one to six days was effected gradually by consuming small excess amounts of the deprived substance.

A number of studies on the effects of oxygen deprivation have recently appeared, no doubt because of its importance in air navigation. Russell (57) gave a group of 244 subjects at a simulated altitude of 18,000 feet a test of finger dexterity, arm-hand coordination, or simple mental arithmetic. The experimenter reports the appearance of a decrement in performance level immediately after the introduction of mild anoxia, and then a rapid adjustment and improvement with continued practice. The data show differences between the experimental and control subjects which appear to be statistically significant. With repeated practice sessions both groups improved, but the differences in performance between the two groups remained relatively constant. Even after both groups were returned to "ground level," the control subjects were usually superior to the experimental subjects.

Similar data were obtained by Green (58), who tested the performance of 50 normal male subjects during four low pressure chamber ascents equivalent to 17,000 feet altitude. Comparisons between ground tests and tests after 60 to 75 min. at high altitudes indicate impairment on all five measures chosen. Peripheral visual acuity (Lloyd stereocampimeter) and simple addition showed losses in excess of 20 per cent; pursuit meter performance and visual acuity tests gave decrements of around 11 per cent; and a sensorimotor test, the Minnesota Block Test, gave a decrement of about 8 per cent.

Smith (59), on the basis of careful and well-controlled experiments, found evidence of some impairment of behavior in 16 college men tested at simulated altitudes of only 10,000 feet. The performance of the same subjects at 1,800 feet served as control data, and the order of the control and test flights was reversed for alternate subject groups. Though no loss of efficiency was found on the Minnesota Block Test during the seven-hour exposure period, statistically significant loss was reported in the perception of speech sounds. Significant loss of efficiency was also indicated in increases in the size of the peripheral blind area of the eye, and in sleepiness, boredom, and wandering of attention. Loss on the tests was usually reduced by an "end spurt" after the fifth hour, although this did not occur for the angioscotoma, the most sensitive indica-

tor of anoxic effects and one relatively free from subjective influence.

Sola, Becker & Windle (60) studied the effect of chronic decompression anoxia on maze retention of guinea pigs. Twenty animals were trained on a simple alternation maze with three blind alleys to the criterion of 10 successive errorless runs, and the 10 experimental guinea pigs were then subjected to decompression anoxia at a simulated atmosphere of 23,000 feet for six hours a day, six days a week. At the end of 100, 250, 300, and 400 hours of decompression, retention tests were run to the original learning criterion, and the performances of the experimental and control animals compared. The authors emphasize that no statistically significant differences either in the trial scores or the error scores appeared, but these "negative" conclusions should be regarded with caution, since the experimental subjects consistently required more trials and made more errors than the controls. The simplicity of the test and its probable low reliability could easily obscure significant behavioral differences.

Drugs and Diet

Tyler (61) has presented a careful and detailed study on the effect of amphetamine sulphate, amytal, and V-12 upon psychological and physiological measures of behavior as they were affected by long wakefulness. Performances following periods of wakefulness ranging from 24 to 112 hr. were studied in a total of 488 men. The effects of the drugs were determined by comparing drug groups with placebo control groups. Insomnia of 110 hr. or longer produced no statistically significant behavioral decrements on flicker fusion frequency tests, tuning fork vibration sensitivity, static ataxia, auditory acuity, estimation of the passage of time, digits span and digits reversed, and the Rorschach test. Multiple choice reaction time and marksmanship gave significant differences when the tests were made long and boresome. Deterioration usually first occurred around the sixtieth hour and could be ameliorated if amphetamine sulphate had been previously given within 12 to 24 hr. and repeated at intervals of 8 to 12 hr. Under these conditions subjects reported a marked decreased difficulty in staying awake, particularly noticeable during the third night. Maintained amphetamine dosage did not give equally favorable results for the fourth and fifth day. Total doses of four grains of amytal or 10 grains of

V-12 did not produce significant deterioration on the tests. Psychological disturbances characterized by irritability, loss of memory, apathy, irrelevant laughter, inattention, illusions, and hallucinations appeared at the second night and continued thereafter. These disturbances were usually mild but in seven cases they became so aggravated as to necessitate removal of the men from the experiment. Following 112 hr. wakefulness the men usually slept for 8 to 14 hr. and after an hour or two of sluggishness appeared to be completely refreshed.

Continuing researches along the line of those previously carried out on dogs, Girden (62) tested the effect of "curarization" (the actual drug used was erythrodine) on conditioned responses in monkeys. Four rhesus monkeys were used as subjects and conditioned responses to both light and bell stimuli were formed in from 10 to 195 trials. The conditioned responses carried over from one drug session to the next and, as previously observed in the dog, there was a functional dissociation in the "curarized" monkeys with the result that drug state learning was completely repressed upon recovery from the drug. Retention of the conditioned responses was demonstrated to persist, in the drugged state, for at least five to six days.

Reiss (63) has presented evidence that maze learning in rats may be facilitated by the injection of adrenal cortical steroid hormones. Forty experimental rats were given intramuscular injections of approximately 0.4 mg. of corticosterone and their performance on a linear six blind-alley Warner-Warden multiple unit tunnel maze was compared with that of 40 control animals. The experimental rats made significantly lower (2 per cent confidence level) error scores over a period of 30 trials and also lower mean error total time scores, the P value being 0.10.

Daily injections of pregnenolone were not found by McGinnies (64) to improve performance on a modified type Stone 14-unit block elevated maze. No significant differences were found between 10 experimental subjects in which 5 mg. of pregnenolone was added to the regular diet of wet mash and 10 control rats fed on wet mash only; indeed the performance of the controls was slightly better than that of the drug group. A second group of six drug rats and six controls were subjected to "cold stress" induced by 75 min. a day of refrigeration at 50° C. prior to the trials on the Stone-type

maze. Cold stress was concluded five minutes before maze running time and the experimental animals were given a daily dosage of 2.5 mg. of pregnenolone. The differences were not statistically significant ($P = 0.10$), but since the groups were very small the author's conclusion that "it is not unlikely that pregnenolone . . . may enhance psychomotor performance under stress" can only be completely demonstrated by further experimentation.

An enthusiastic account of the benefits derived from supplementing the diet of orphanage children by added thiamine has been presented by Harrell (65). Performance was measured by a battery of 15 tests ranging from height and weight to the CAVD intelligence test. The pre-experimental average thiamine intake of the children was computed as 1 mg. of thiamine per day. Fifty-five matched pairs of children served for a one-year period as subjects, one member of each pair receiving a daily tablet of 2 mg. of thiamine and the other a placebo. Twenty-seven pairs were maintained under the same conditions for another year, while in 20 pairs the drug-placebo conditions were reversed. The thiamine group at the end of the first year was superior on the 15 tests used and the differences were statistically significant on eight. No significant gain was found on any of the three intelligence-achievement tests. Striking differences were apparent in visual acuity, retention, memorization, and code substitution tests. At the close of the second year the thiamine supplemented group still showed superior gains in all performances, whereas the reversal groups showed reversal of gains in eight activities, not including measures of intelligence, educational achievement, reaction time, or height and weight.

Hamilton & Maher (66) found no statistically significant differences in number of perfect trials or total errors on the Maier 3-table reasoning test between 25 control rats fed on a bread and milk diet and 24 experimental rats in which the bread and milk diet was supplemented by 275 mg. L(+)-glutamic acid. The experimental rats did show higher activity levels and obtained the food in less time. No significant differences were found between the two groups in emotionality as measured by the Anderson water-wading test, or susceptibility to electric seizures.

Similar results were obtained by Marx (67) in a careful and well-controlled experiment. A group of 56 rats had the normal diet sup-

plemented by a 1 cc. solution containing 200 mg. L(+)-glutamic acid daily. The solution was directly injected through the mouth deep into the esophagus by a syringe. A control group of 33 rats received only the basic diet and a second control group received the basic diet and 1 cc. of water with 200 mg. of glycine. No significant differences were found in the learning or relearning by the three groups of a modified Stone multiple-T water maze with 14 choice points. In actual fact, the controls were slightly superior to the experimental subjects. Though the results give no evidence that supranormal glutamic acid feeding improves learned performance, the author stresses the fact that further work must be done before we can be certain of the mental effects of this dietary factor.

LITERATURE CITED

1. FREEMAN, G. L., *Physiological Psychology*, 550 pp. (D. Van Nostrand Co., New York, 1948)
2. ADRIAN, E. D., *The Physical Background of Perception*, 95 pp. (Clarendon Press, Oxford, England, 1947)
3. GARDNER, E., *Fundamentals of Neurology*, 336 pp. (W. B. Saunders, Philadelphia, 1947)
4. FULTON, J. F., *Howell's Textbook of Physiology*, 1304 pp. (W. B. Saunders, Philadelphia, 1946)
5. KANTOR, J. R., *Problems of Physiological Psychology*, 398 pp. (Principia Press, Bloomington, Indiana, 1947)
6. CAMPBELL, R. J., AND HARLOW, H. F., *J. Exptl. Psychol.*, **35**, 110–26 (1945)
7. WADE, M., *J. Neurophysiol.*, **10**, 57–61 (1947)
8. SETTLAGE, P., ZABLE, M., AND HARLOW, H. F., *J. Exptl. Psychol.*, **38**, 50–65 (1948)
9. WARD, A. A., *J. Neurophysiol.*, **11**, 13–23 (1948)
10. VAN WATERS, R. O., AND SACKS, J. G., *J. Psychol.*, **25**, 73–88 (1948)
11. KISKER, G. W., *Psychiat. Quart.*, **18**, 43–52 (1944)
12. PORTEUS, S. D., AND PETERS, H. N., *Genetic Psychol. Monographs*, **36**, 3–86 (1947)
13. FREEMAN, W., AND WATTS, J. W., *Digest Neurol. Psychiat.*, **16**, 62–68 (1948)
14. HALSTEAD, W. C., *Brain and Intelligence, a Quantitative Study of the Frontal Lobes*, 206 pp. (University of Chicago Press, Chicago, 1947)
15. BROMILEY, R. B., *J. Comp. Physiol. Psychol.*, **41**, 155–64 (1948)
16. MOSS, E., AND HARLOW, H. F., *J. Psychol.*, **25**, 223–26 (1948)
17. BROMILEY, R. B., *J. Comp. Physiol. Psychol.*, **41**, 102–10 (1948)
18. SPERRY, R. W., *J. Neurophysiol.*, **10**, 275–94 (1947)
19. SMITH, K. U., *J. Exptl. Psychol.*, **37**, 367–76 (1947)
20. SPERRY, R. W., *Quart. Rev. Biol.*, **20**, 311–69 (1945)
21. SPERRY, R. W., *Anat. Record*, **97**, 293–316 (1947)
22. SPERRY, R. W., *Arch. Neurol. Psychiat.*, **58**, 452–73 (1947)
23. SPERRY, R. W., *J. Comp. Psychol.*, **39**, 321–30 (1946)

24. SPERRY, R. W., *J. Neurophysiol.*, **8**, 15–28 (1945)
25. LASHLEY, K. S., *Psychol. Rev.*, **54**, 325–34 (1947)
26. DUSSER DE BARENNE, J. G., AND MCCULLOCH, W. S., *J. Neurophysiol.*, **4**, 304–10 (1941)
27. MCCULLOCH, W. S., *Bull. Math. Biophys.*, **7**, 89–93 (1945)
28. MCCULLOCH, W. S., AND PITTS, W., *Bull. Math. Biophys.*, **5**, 115–33 (1943)
29. ROSENBLUETH, A., WIENER, N., AND BIGELOW, J., *Philosophy Sci.*, **10**, 18–24 (1943)
30. APTER, J. T., *J. Neurophysiol.*, **9**, 73–86 (1946)
31. PITTS, W., AND MCCULLOCH, W. S., *Bull. Math. Biophys.*, **9**, 127–47 (1947)
32. JONES, F. N., *Am. Psychol.*, **3**, 339–40 (1948)
33. STONE, C. P., *Proc. Soc. Exptl. Biol. Med.*, **61**, 150–51 (1946)
34. DUNCAN, C. P., *J. Comp. Physiol. Psychol.*, **41**, 11–16 (1948)
35. MCGINNIES, E., *J. Comp. Physiol. Psychol.*, **40**, 31–36 (1947)
36. ERIKSEN, C. W., PORTER, P. B., AND STONE, C. P., *J. Comp. Physiol. Psychol.*, **41**, 144–54 (1948)
37. HAYES, K. J., *J. Comp. Physiol. Psychol.*, **41**, 40–61 (1948)
38. PORTER, P. B., AND STONE, C. P., *J. Comp. Physiol. Psychol.*, **40**, 441–56 (1947)
39. HOROWITZ, M. W., AND STONE, C. P., *J. Comp. Physiol. Psychol.*, **40**, 15–21 (1947)
40. STONE, C. P., *J. Comp. Physiol. Psychol.*, **40**, 183–89 (1947)
41. ZUBIN, J., in *Methods of Psychology*, Chap. 20 (Wiley & Sons, New York, 1948)
42. MAIER, N. R. F., FELDMAN, R. S., AND LONGHURST, J. U., *J. Comp. Physiol. Psychol*, **40**, 73–86 (1947)
43. MAIER, N. R. F., AND LONGHURST, J. U., *J. Comp. Physiol. Psychol.*, **40**, 397–412 (1947)
44. LAZOVIK, A. D., AND PATTON, R. A., *J. Comp. Physiol. Psychol.*, **40**, 191–202 (1947)
45. PATTON, R. A., *J. Comp. Physiol. Psychol.*, **40**, 323–32 (1947)
46. PATTON, R. A., *J. Psychol.*, **24**, 313–17 (1947)
47. PATTON, R. A., *J. Comp. Physiol. Psychol.*, **40**, 283–89 (1947)
48. SIEGEL, P. S., AND STUCKEY, H. L., *J. Comp. Physiol. Psychol.*, **40**, 365–70 (1947)
49. SIEGEL, P. S., *J. Comp. Physiol. Psychol.*, **40**, 231–38 (1947)
50. BINDRA, D., *J. Comp. Physiol. Psychol.*, **40**, 149–56 (1947)
51. BINDRA, D., *J. Comp. Physiol. Psychol.*, **41**, 211–18 (1948)
52. HUNT, J. MCV., SCHLOSBERG, H., SOLOMON, R. L., AND STELLAR, E., *J. Comp. Physiol. Psychol.*, **40**, 291–304 (1947)
53. MORGAN, C. T., *Psychol. Rev.*, **54**, 335–41 (1947)
54. YOUNG, P. T., *J. Comp. Physiol. Psychol.*, **40**, 37–72 (1947)
55. PILGRIM, F. J., AND PATTON, R. A., *J. Comp. Physiol. Psychol.*, **40**, 343–48 (1947)
56. ADOLPH, E. F., *Am. J. Physiol.*, **151**, 110–25 (1947)
57. RUSSELL, R. W., *J. Exptl. Psychol.*, **38**, 178–87 (1948)
58. GREEN, D. M., *Am. J. Physiol*, **151**, 588–92 (1947)
59. SMITH, G. M., *J. Gen. Psychol.*, **38**, 3–14 (1948)
60. SOLA, A. E. ,BECKER, R. F., AND WINDLE, W. F., *J. Comp. Physiol. Psychol.*, **41**, 196–202 (1948)

61. TYLER, D. B., *Am. J. Physiol.*, **150**, 253–62 (1947)
62. GIRDEN, E., *Am. J. Psychol.*, **60**, 571–87 (1947)
63. REISS, B. F., *J. Comp. Physiol. Psychol.*, **40**, 8–11 (1947)
64. MCGINNIES, E., *J. Comp. Physiol. Psychol.*, **40**, 389–96 (1947)
65. HARRELL, R. F., *Teach. Coll. Contrib. Educ.*, No. 928, 102 pp. (1947)
66. HAMILTON, H. C., AND MAHER, E. B., *J. Comp. Physiol. Psychol.*, **40**, 463–68 (1947)
67. MARX, M. H., *J. Comp. Physiol. Psychol.*, **41**, 82–92 (1948)

MUSCLE*

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In this review the author's primary interest is in studies concerned with fundamental problems of contraction of skeletal muscle. Although this limitation reflects the taste of the reviewer, it is also determined by the space restrictions within which this article must be written. Fortunately, some of the topics that will not be considered have been brought almost up-to-date in other recent reviews. The reader is referred to the papers of Buchthal (1) and Eccles (2) for consideration of muscle permeability and neuromuscular transmission, and to the papers of Grundfest (3) and Bremer (4) for further treatment of the latter subject. In addition to Wilbrandt's (5) earlier summary of permeability it may be expected that Teorell (6) will cover the most recent work on muscle in this field. Only incidental attention will be given to smooth and cardiac muscles, muscle metabolism, kinesiology, electromyography, and myopathies.

The basic papers encompassed by the present review, excepting a number of significant but previously untreated publications, have appeared in the period from April, 1946, to July, 1948. Although during this time some notable advances have been made in our knowledge of muscular contraction itself, the muscle physiologist is, however, struck by the increasing attention he must pay to research dealing with the extracted nonliving actomyosin system, evidently the essential contractile material, and with the mechanochemical coupling of this system with adenosinetriphosphate (ATP). These studies of muscle extractives, stemming from the pioneer investigations of the biochemists Englehardt and Szent-Györgyi [see (1) for references], are undoubtedly of greatest importance; but, as will be seen later, the physiologist must exercise great caution in applying the biochemical findings to the solution of the problems of muscular contraction.

Before entering into the detailed discussion of the individual

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papers germaine to this review, attention should be called to a symposium on muscular contraction held under the auspices of the New York Academy of Sciences. Particular references to the various contributions of this publication will be discussed later, but the general scope of the symposium is of interest and is indicated by the subjects it covered: dynamics (7 to 10), ultrastructure (11, 12), chemistry (13, 14), and mechanochemical coupling (15 to 18). Of general interest also are Dubuisson's stimulating review (19), which presents an interesting integration of the chemical and physical events associated with contraction and which should be read in close conjunction with Meyerhof's study (13), and Singh's analysis (20) of the comparative physiology of unstriated, cardiac, and skeletal muscle.

It is noteworthy that despite seemingly insuperable dislocations resulting from the recent war, a number of European laboratories, especially in Denmark, Hungary, Belgium, and England, have produced much work of fundamental importance. Some of this research was done during periods of Nazi occupation under conditions of extreme deprivation and even personal hazard. It is with a certain humility that we express admiration for the courageous and steadfast devotion to science of our European colleagues that made these advances possible and thus continued in a world torn with conflict the high internationalism of scientific endeavor.

Mechanics

Recording technique.—New electrical and electronic methods for registering mechanical changes, in certain cases involving the cathode-ray oscillograph for ultimate recording, characterize many recent studies. Some attention has already been given (1) to the condensor myograph in the investigation of single fibers [(21 to 24); see also (25)] and to the piezoelectric pickup for registration of the minute mechanical alterations during the latent period (26). Further various utilizations of the piezoelectric technique have been made for direct recording of muscle responses (18, 27 to 30) and, by using electronic differentiation, for obtaining the first time derivative of the tension output throughout the course of the twitch (31). A special strain gauge (32) and condensor and carbon microphones (33, 34) have been employed as pickups for either direct or differentiated registration. In general, these methods possess certain advantages over conventional myographic tech-

niques, among which are: maintenance of almost perfect constancy of muscle length in isometric contractions, extreme sensitivity (e.g. considered as an electronic lever, the piezoelectric, cathode-ray oscillographic myograph has a magnification factor of the order of $10^6\times$), negligible inertia, and, where especially the cathode-ray oscillograph is used, immediate visualization of the muscle's mechanical behavior in either direct or differentiated form.

Single fibers.—Barer (35), with remarkable integration, clarity, and acumen, has reviewed research from a wide variety of fields on the structure and certain related aspects of the function of the striated muscle fiber. Some general conclusions of this study (which should be consulted for pertinent references) are relevant to the present discussion. The muscle fiber consists of a bundle of myofibrils embedded in a viscous medium, the sarcoplasm, the whole being surrounded by a delicate sheath, the sarcolemma, which is differentiated from the adventitious connective tissue element that has been designated by other workers as the sarcolemma and is held responsible for the resting tension of the fiber (7). It is still unsettled whether the sarcoplasm possesses contractility, but impressive evidence is presented to support the view that the myofibrils not only are contractile, but that they also exist as such in the normal living fiber. According to Barer, there does not seem to be any, at least histologically demonstrable, structure such as the supposed Z, or Krause's, membrane that might serve to connect individual myofibrils to each other, on the one hand, or myofibrils and sarcolemma, on the other. This raises the perplexing problem of the nature of the mechanical coupling between the intrafibrillar contractile material and the sarcolemma through which finally the contractile force must be transmitted to the tendons. It is speculated that such coupling could be effected by frictional or viscous forces (which, the present reviewer wishes to add, might have their source in mechanisms similar to the fibrillar surface, long range colloidal, and hydrogen-bond forces indicated by Barer to account for the well-known quite perfect alignment of the striations). Barer's hypothesis has also been put forward by Bull (36) in his picturesquely termed "fluid-drive" mechanism and this is discussed with certain reservations by Guth (9).

Insufficient attention has been given in these reviews to Ramsey's provocative treatment (37) of single fiber physics published in 1944. Based principally on a mathematically quite simplified

formulation of the length-isometric developed tetanus tension diagram in the region only of the shorter lengths up to that which gives maximum tension, and the experimentally rather justified assumption that the rate of shortening in isotonic tetanus is not constant as supposed by Hill (38), but rather decays exponentially as shortening proceeds, the analysis leads to certain quantitative predictions concerning heat (shortening and maintenance) and work outputs that are in good agreement with experiment. Strikingly, the theory also permits formulation of a force-velocity relation essentially similar to Hill's and suggests certain correlations to Astbury's conceptions of the states of folding of myosin. A major difficulty of the general basis of the theory, however, is its inability to handle the length-tension relation at lengths greater than that which yields maximum developed tension. More recently (7), Ramsey proposes a new formula for the entire length-tension curve, though this is not developed in relation to the earlier theory, and he presents data indicating that the delta-state of the striated fiber is similar to normal smooth muscle.

Høncke (25), after presenting a very useful general review of work on the single fiber, extends the research of the Buchthal school (1) to a comprehensive study of the structure and function of mammalian (mostly guinea pig) striated muscle cells. Apart from the presence of a lower resting elasticity modulus and the same stiffness during contraction as at rest (when referred to the same tension), he finds that these elements and their striations have essentially the same mechanical (and birefringent) properties as those of the frog fiber. The validity of the interpretations of some of the results concerning resting elasticity and the effects of stretches and releases, suddenly applied during contraction, of this and its background research depend on the assumption that the resting tension of a fiber is attributable mainly to the intrafibrillar material. It is therefore evident that unequivocal interpretations are not possible in all cases as long as the question of the source of resting fiber elasticity continues to be a subject of controversy. Ramsey (7) still forcefully holds that the sarcolemma is responsible for the resting tension and Buchthal (1), taking a position with which the reviewer completely agrees, states that "this question requires further experimental investigation."

Latency relaxation.—A previously unnoted demonstration of the minute latency relaxation (LR) in mammalian muscle should be

mentioned (34). The compression-wave artifact interpretation of the LR advanced by Gilson *et al.* (8, 27) has been shown to be invalid in experiments of the author (18, 39, 40) and Abbott & Ritchie (30). The experiments were performed in a variety of ways so that compression wave effects, if they exist at all, could not possibly contribute to the underlying forces leading to the production of the latency mechanical changes. For example (18, 39), massive transverse stimulation was used and this results in practically simultaneous initiation of the mechanical response at all levels along the entire muscle length thus eliminating the compression wave. Nevertheless, transverse recording at each level shows that the earliest manifestation of mechanical change throughout the entire muscle length is the latency elongation. The alleged compression wave behavior of a water-filled rubber finger cot, supposed by Gilson *et al.* to be analogous to the artifact mechanism of the LR, could not be demonstrated in experiments in which a sartorius muscle replaced the finger cot (18) and, moreover, the finger cot result has itself been shown to be an artifact due to the use of a very long pickup stylus (40). It is therefore evident that the latency relaxation cannot be considered as a compression wave artifact.

Barer (41), however, proposes the possibility that LR develops because of a sarcolemma stretching due to a slippage between the sarcolemma and the underlying contracting muscle substance. But this view is quite speculative since it depends on an assumed mechanism for the still highly controversial means by which the contractile substance is coupled to the sarcolemma; and it is offered without either experimental support or means for testing it. Furthermore, it is difficult to see how the assumed stretching of the sarcolemma would result in a relaxation of the fiber, since the stretch, although causing an elongation, would involve operation of a tension that should phenomenologically appear as contraction and not a relaxation.

Since the various artifact interpretations of the LR do not seem tenable, it is reasonable to assume that the LR is an expression of the initial mechanical reaction of the contractile system in a stimulated muscle, and this validates speculations regarding its underlying mechanism. The suggestion that the LR signifies the formation of an intermediate complex between myosin-adenosinetriphosphatase and ATP (18) is supported by Engelhardt (42) and

Dubuisson (19). The latter also calls attention to the synchronization of the LR with the initial alkalinization that has been observed in responding muscle and which may be likened to the pH-increase that has been detected in muscle subjected to passive elongation. Bull (36) proposes an LR mechanism involving rupture, immediately following stimulation, of hypothetical longitudinal stabilizing linkages of resting myosin. It must be borne in mind that these conceptions are only inferences and that the actual process causing the mechanically observable LR behavior has yet to be discovered.

Human muscle.—The mechanics of essentially isolated human skeletal muscle has been studied by Ralston *et al.* (32, 43) in amputees having cineplastic tunnels in various arm and chest muscles, and these properties have been found in many respects (load-work, resting length-tension, and isometric contraction length-tension curves) to be similar to those of isolated frog muscle behavior. For relatively slow and uniform contractions the shortening of the free-loaded muscle is a linear function of the load and this leads mathematically to a parabolic relation between load and work like that found experimentally in general. The relation between the velocity and load in human, voluntary normal arm flexions has been analyzed by Dern (44) in reference to Hill's formula (38) connecting these variables in the activity of isolated muscles. These flexions are shown to be complicated by both the temporal and topographical pattern of innervation of the arm musculature—electromyographical tests, for example, indicating involvement of antagonists. It is concluded that the speed of human limb movements is not governed solely by the basic contractile mechanism and, therefore, cannot be expressed by Hill's relation.

Kinetics.—Kinetic theories of contractions are presented in reviews by Ramsey (7) and Gilson *et al.* (8). A new approach is developed by the author (18) in which a basic assumption is made that a chain of four first-order reactions involving transformations of four forms of the contractile material (myosin) underlies the output of tension in both twitch and tetanus. In contrast to the purely empirical evaluation of constants characteristic of the formulations of Ramsey, and Gilson *et al.*, the new analysis involves a semiempirical method dependent on certain considerations of the latency relaxation and the rates of rise and fall of tension in isometric tetanus. The new theory thus calculates the form of the twitch from that of the tetanus, which is opposite to the attempt of Gilson *et al.* to determine the course of the tetanus from that of the twitch.

The reviewer's procedure leads to rather good agreement between theoretical and experimental twitch and tetanus curves (which include not only the usual contraction and relaxation periods, but the latency relaxation, as well). But this procedure necessarily requires that a single shock release a tension producing process that is potentially capable of developing full, i.e., tetanic, tension and this does not seem to agree with present experience [see, however, Hill (38)]. It is interesting to note that the theories of Gilson *et al.* and of the reviewer, despite their differences, are alike in assuming in the excited muscle a reaction chain of first-order reactions. They are also similar in regard to the position of the tension producing substance in the reaction chain, for, according to the author, this material is the fourth in the series, and Gilson *et al.* state that "the substance critical for tension development must occur later than the second in the chain of limiting reactions." These inferences despite their being grounded merely in kinetic analyses of mechanical responses, yet strongly indicated that a rather complex series of reactions run their course during the latent period in order to link the immediate effect of the stimulus to the actual tension causing process.

Chemically induced, and activated alterations in contractility.—In an intricately conceived series of experiments, carefully controlled so as to distinguish between excitability and contractility changes, Walker (45, 46, 47) has investigated the electrical, as well as contractile, responses of the variously stimulated *in situ triceps surae* muscle of normal, adrenalectomized, desoxycorticosterone (DCA)-treated, and potassium chloride-treated rats. The limitations of our review do not permit full discussion of the many complexly interwoven results of these papers [or of Walker's related publications (48, 49) dealing with neuromuscular transmission]. Of great interest however, is the clear demonstration of marked increases of intrinsic twitch contractile strength under the following various conditions: in rested muscles of animals injected with potassium (80 mgm. per 100 gm.); during treppe in muscles of both normal and adrenalectomized animals; and in post-tetanic potentiation (PTP) of rested muscles of normal, potassium- and DCA-treated, and adrenalectomized animals, and in only normal already fatiguing muscles. Although increase in intracellular potassium leads to greater twitch tension output, it is curious that DCA-treatment, which reduces intramuscular potassium, does not modify PTP in the rested muscle. (DCA, however, causes diminished

twitch tension following tetanus in fatigued muscle.) Despite the enhancing effects of potassium and adrenalectomy on the twitch tension, it is significant that the tetanus tension under these altered conditions is essentially the same as that produced by normal muscles. This seems to prove that increased intramuscular potassium caused, either by direct application of potassium or by adrenalectomy, leads to a greater mobilization of force following a single shock, but that the peak tetanus tension cannot be modified by such treatment.

That PTP is a property of the muscle contractile substance and not due, e.g., to repetitive discharges or recruitment of pretetanic inactive fibers had already been indicated by Ramsey & Street (50) in PTP experiments on isolated muscle fibers of the frog. Walker's observation that PTP is not impaired by complete curarization is not in accord with earlier results on frog material (51, 52), but in confirmation of Walker's finding the reviewer in unpublished experiments has demonstrated PTP in the curarized frog sartorius.

The characteristic action of epinephrine in increasing the twtich tension of mammalian fatigued muscle is attributed by Brown *et al.* (53) to its direct effect on the tension developed in the individual fiber, and this enhancement has been shown to depend on the presence of a relatively high value of the intracellular to extracellular potassium ratio (54, 55).

To the above results, evidently indicating the importance of potassium in determining the contractile power of muscle, may be added a number of other contributions (56 to 62). In particular reference to Walker's work, it is also of interest that, in rats, Hoagland & Stone (63) report new findings that DCA reduces intramuscular potassium (and also augments the decrease of muscle potassium due to exercise) while adrenalectomy greatly increases potassium in muscle, and that Trowbridge & Jordan (64), contrary to an earlier conclusion of other workers, have found that changes in potassium distribution due to adrenalectomy leave unchanged the potassium loss from contracting muscle. Thus, many new facts have been added to the already bewildering mass of evidence concerning the behavior of potassium in muscular function, but despite the importance of many of these findings we seem to be as far as ever from understanding the role of this ion in contraction.

Probably, as the work of Hoagland & Stone (63) and Goffart &

Brown (54, 55) indicates, more attention should be paid to the intracellular-extracellular potassium ratio. But, since this is generally regarded as affecting excitability, it may be more significant, as stressed by Steinbach [in an extremely valuable review (16) of the relation between intracellular inorganic ions, in general, and muscle action], to study absolute intracellular potassium concentrations in attempting to elucidate the role of potassium in contractility. In this regard, we note the findings of Heilbrunn and his students (65, 66) that potassium has little effect on the shortening or clotting of muscle cytoplasm, either when injected into the fiber or allowed to act by diffusion through the cut ends. But these experiments were done on resting fibers, and it would be of great interest for the comprehension of contractility to study the effect of electric stimulation acting in combination with such potassium treatment of muscle protoplasm.

A study of the ankle jerk in cases of human myxedema (67) has demonstrated that the participating muscles show greatly prolonged contraction and relaxation periods which are not due to the slightly lower temperatures of the muscles. These effects and those previously discussed in relation to adrenal function clearly prove the important role, and the desirability of further study, of the endocrine system in the control of muscular function in the intact animal.

Other studies of augmented muscular strength have appeared: PTP in unfatigued normal, iodoacetate, and potassium cyanide muscles in which the potassium cyanide results are of special interest (68); potentiation following short rests in fatiguing muscle showing a curious secondary as well as a primary period of enhancement (69); and after-stretch potentiation (70) which seems to be in contradiction to the report (50) that a stretch intercalated during PTP does not affect this type of augmentation in single fibers.

Elasticity.—Some general aspects of this topic have already been considered in the section on single fibers. Schoepfle & Gilson (71), using a new quick release method, present evidence that the elastic properties of the turtle retractor penis muscle are unaffected by contraction. This leads to the inference that the intrafibrillar material as a whole remains plastic during a twitch and, therefore, that actively developed axial tension is attributable to an anisometric change in protoplasmic ultrastructural units such that a

lateral pressure is directed against the sarcolemma in which, in turn, there results the generation of the longitudinal tension of a contraction. Although some corroborative evidence is adduced in favor of this hypothesis of tension development, it is not unequivocal. However, the basic experimental conclusion, although corroborated in experiments on single mammalian fibers (25), is not in agreement with the results of Buchthal (1) on single frog fibers, and its validity has been seriously and rather convincingly questioned on several grounds by Ralston *et al.* (32). Of some relevance to this question is the result found in a study of the torsional elasticity of isolated frog fibers that the directional couple is much higher during contraction than at rest (72). In a study (73) employing the Hill dynamical spring method it is shown that within the successive states of tetanus of a series of 5 sec. tetani both the elasticity and the viscosity coefficients at first rise and then fall in both normal and iodoacetate muscles, but within the intervening states of rest of such tetanic series, although in the normal muscle both coefficients essentially fall, in the IAA muscle, they first fall and then rise.

In confirmation of the results of Erdös (74), Bate-Smith & Bendall (75) demonstrate that in association with the onset and development of rigor mortis of rabbit muscle there is a parallel increase in stiffening and decrease in adenylpolyphosphates, specifically interpreted as ATP. This correlation occurs both in normal acid and in alkaline rigor, the latter appearing in muscles initially deprived of glycogen. Shortening occurs only if the pH of the muscle exceeds about 6.2 as stiffening sets in, and it is noteworthy that such shortening develops an absolute force of only about one-twentieth of that generated in voluntary contraction.

At this point only mention will be made of Guth's comprehensive and informative review on muscular contraction and rubber-like elasticity (9) and Bull's suggestive discussion of the elastic element of skeletal muscle (36). Certain features of these papers will be discussed in a later section dealing with the energetics of the ultrastructural components of muscle.

Myothermy

The study of heat output of muscle, which has been in abeyance for some time, is being resumed. In Hill's laboratory, a radically improved myothermic apparatus has been constructed which utilizes a new galvanometer of only five milliseconds period in con-

junction with vacuum tube amplification, and dual beam cathode-ray oscillographic recording of not only the thermal changes but also the mechanical changes (76). The chief result to date is that heat production in a twitch has already reached a high rate at the termination of the latent period. This finding and the evident possibilities of the new apparatus are of greatest portent for muscle physiology. Aubert (77) utilizes a novel approach to the problem of thermodynamic reversibility of contracting muscle in an investigation comparing the over-all heat and work transformations in a Levin-Wyman (78) complete work cycle with the heat production of a maintained isometric contraction having the same duration as the cycle and the same muscle length as that common to the initial and final points of the cycle. He has found that, if the initial length is not too great, the heat output of the cycle is less than that of the corresponding isometric activity and this indicates what may be called an inverse Fenn-effect, i.e., during the elongation phase of the work cycle, the muscle, instead of liberating extra heat, as it does in the shortening, absorbs some of the energy of the external work that has been applied to it and stores it in an elastic potential form. It is therefore concluded that, at least partially, muscular contraction is thermodynamically reversible and this suffices to explain elastic hysteresis without reference to viscous phenomena. Aubert has also studied certain cases of activity in which a true Fenn-effect exists, though it is masked by other heat relases (79).

Small changes in "efficiency" (ratio of twitch tension to initial heat) have been found in post-tetanic potentiation, but are not considered to be adequate to account for the mechanical changes (80). Some interesting findings are reported regarding heat output of human muscle in a cutaneous-muscular reflex (81) and in voluntary contraction (82).

Bioelectricity and Excitability

Resting potentials.—Further evidence favoring the potassium diffusion potential theory of the membrane potential of the frog muscle cell is found in the results of Shanes (83) that cocaine, which reduces the permeability of cells to potassium, greatly reduces the depolarizing power of externally increased potassium concentrations, and in the finding of Ling (84) that the average value of the true membrane potential, as measured with microelectrodes, is 77.5 mv. which is close to that predicted by theory (85). Tobias'

report (86) of anomalous behavior of frog muscle soaked for many hours in distilled water to cause potassium depletion of the fibers, although of intrinsic interest, can hardly apply to the properties of the normal membrane potential since the fibers were dead.

It has been found that stretch of the single frog fiber does not alter its membrane potential (84). This is contrary to determinations made of frog muscle injury potentials (87, 88), but no discrepancy may be involved since the positive effect of stretch was found to decrease with time and to be small for large extensions (88). However, in connection with the general problem of the effect of stretch on the electric potentials of both resting and active muscles, some early papers of de Meyer should be read (89).

Excitation and conduction.—Several papers present new evidence concerning the perennial problem of the role of potassium in excitability (90 to 93). Walker (45, 46) adds to this his result that repetitive discharges occur in rat gastrocnemii in animals treated with DCA and fed a low potassium diet. Surprisingly long survival of direct excitability (up to 29 days) is reported in frog muscle kept at 0°C. (94). A number of curious and interesting findings have appeared in research on the excitability of gastrocnemii in rats and cats to tetanic direct and indirect stimulation; e.g., large tetanic contractions may be excited by indirect stimulation when "fatigue" has already set in due to direct excitation (95). Bock (96) reports changes in muscle excitability associated with extinction of make excitation by oppositely directed currents.

Observations have been made of triple contractions and triple chronaxies in normal mammalian, including human, striated muscle (97). Curariform effects of veratrine on muscle threshold are presented by Jaques (98). Szepsenwol (99, 100) has determined changes in electrical threshold of chick skeletal and heart muscle fibers developing in tissue culture explants. In studies of the local and conducted potentials of smooth muscle subjected to stretch, Bozler (101) concludes that the presence of the former always before the latter proves the muscular origin of visceral smooth muscle activity. Eyster & Gilson (102) have investigated electrical changes of loci of heart muscle injured by suction which indicate that variations in amplitude and polarity occur at the injured region when the surrounding muscle enters into activity.

Katz & Lou have published results concerning electric rectification in frog's muscle (103) and stimulation with transverse al-

ternating current shocks (104). The findings of the latter investigation, and those dealing with the activation of contraction by means of massive transverse direct current shocks (18, 39, 40), raise some interesting problems concerning the fundamental mechanism of excitation, the discussion of which will be omitted in view of the present primary interest in contractile phenomena.

Chemical events and conduction.—The Nachmansohn conception of the role of acetylcholine (ACh) in conduction [see Grundfest (3) for a penetrating review] has been extended to muscle fibers (105). In curarized frog sartorrii, it has been determined that, as in nerve, penetrating anticholinesterases[di-isopropylfluorophosphate (DFP) and eserine] cause a considerable and somewhat reversible depression of the muscle action potential, while the nonpenetrating inhibitor, prostigmine, causes only a slight decrement. The presence of choline acetylase in skeletal and cardiac muscle, and its absence in liver and kidney (106), and the interference with both direct electrical and ACh stimulation of striated muscle by DFP and its chlorine analogue (107) furnish added evidence supporting the ACh mechanism in muscle conduction. The finding (108), nevertheless, that DFP potentiates the response of the frog rectus abdominis muscle to ACh should not militate against the hypothesis, since in these experiments the DFP was used in very low concentrations and its potentiating effect was markedly dependant on the use of an unbuffered DFP solution having a quite low pH. Of further interest to the problem of the chemical events in conduction, and excitation, also are Scheiner's (57, 109, 110, 111) and Scheinfinkel's (112, 113) results dealing with certain striking differences between electrical and chemical stimulation of striated muscle.

Membrane properties and contraction.—One of the most provocative mysteries in muscle physiology is the mechanism by which excitatory changes are linked to the contractile process. Kuffler (10, 114) has given us some insight to this problem by his work on the membrane potentials correlated with chemical and electrical contractures, which clearly indicates that it is not the currents associated with action potential transmission which serve to initiate the events leading to contraction, but rather the depolarization, as such, of the muscle fiber membrane. Corroboratory evidence for this view is found in the twitch-like responses of novocaine-treated muscle stimulated with massive transverse shocks, for here the

drug, although blocking conduction, does not suppress depolarization (39). For further discussion of this general problem, especially in relation to end-plate potentials, refer to Eccles' review (2).

Zawadski (115), in experiments recalling similar work by Bishop & Gilson (116), seems to have demonstrated that a section of muscle treated with distilled water, ether, chloroform or aniline, is excitable and conductive, but not contractile, thus separating excitability from contractility.[1] It would be desirable to repeat these experiments with a more sensitive technique involving present-day methods of recording both action and resting potentials.

Ultrastructure, Enzymology, and Mechanisms of Contraction

In recent years a quite voluminous body of results has appeared on the ultrastructure of muscle and certain closely connected enzyme reactions, upon which hypotheses of the mechanical behavior of muscle have been formulated. The discussion of this material will be concentrated on the aspects of the subject which at present seem to have significance for muscle activity and will thus only incidentally treat research having purely biochemical or colloid chemical interest. Although some of the findings have only structural significance, many deal with the mechanochemistry of muscle systems and it is these that have by far the greater interest for the muscle physiologist. This is made clear in Engelhardt's discussion (42) of mechanochemistry as

> the study of physical changes of the contractile substance which are obviously related to its mechanical properties and are induced by chemical agents, products of the functional metabolism of muscle tissue. The main theme of such research is clear. The newly found enzymic action of myosin cannot occur unless a combination of ATP with myosin takes place, to form a complex of the usual enzyme-substrate type. ATP is the bearer of the chemical energy generated in the course of metabolic processes and accumulated in the form of energy-rich phosphate bonds. Myosin is the principal bearer of mechanical properties of the muscle fiber. The fact that an interaction of these two substances has been shown to occur suggests that this very interaction is responsible also for the physical changes of myosin which finally manifest themselves in the form of muscular work. Experimental evidence has shown conclusively that these expectations, derived from the results of enzymic studies, are correct.

It will be seen that this delineation of the field of mechanochemistry and its significance is, in essence, still correct, although more

[1] I wish to thank Dr. M. A. Rudzinska for translating this article from the Polish.

attention to actomyosin, rather than myosin, as the bearer of the mechanical properties of muscle seems to be required.

Of considerable interest in this field is the appearance of two books by Szent-Györgyi (117, 118) summarizing the investigations of his school. The latter of these two works is essentially a revision in more compact form of the earlier one, but it also contains new material on the protins, the nature of cross-striation, and the highly controversial continuum theory. However, it unfortunately lacks detailed bibliographic references. As pointed out by Meyerhof (119) and Bailey (120) in critical reviews of the earlier volume, which are equally applicable to the second, there is much important and enduring fact and stimulating discussion in this work; but there is also some questionable interpretation of purely chemical experimental results (especially see Bailey's review in this respect), and considerable shifting speculation that is frequently insufficiently differentiated from fact. It should also be noted that Szent-Györgyi is quite prone to use a teleological method by which imagined mechanisms based on preconceptions of purpose to be served are assumed with rather startling finality to be valid explanations of physiological processes. Furthermore, some confusion has been engendered, at least in the unwary, by the undoubtedly unintentional implication expressed, e.g., in the titles of the above-mentioned studies, that the underlying research deals with physiological muscle, although, actually, it is concerned with either quite dead muscle fibers which in certain cases have been thoroughly macerated, or with highly simplified model systems composed of various muscle extractives.

Rather more sober and still very stimulating reviews will be found in papers by Astbury (121, 122, 123), especially involving x-ray studies, in Bailey's short but highly informative summary discussions of muscle proteins (124, 125), and in the reports of Fischer (11), Schmitt *et al.* (12, 126), and Barer (35).

Ultrastructure.—The protein composition of the muscle fibril is becoming very complex indeed. Not only do we have the currently accepted myosin, actin, actomyosin, tropomyosin, and paramyosin, but now Banga *et al.* (127) [see also (118)] announce the discovery of possibly six new "protins" which are normally adsorbed on a myosin skeleton to fashion a "myosin system." It is claimed that only the system possesses enzymatic and contractile power, and a variety of enzymatic functions have been attributed to the various protins. The protins, furthermore, are all acid- and

heat-stable, a property reminiscent of Kalckar's myokinase (128). The reader should, however, read Bailey's reservations (120) concerning the existence of accessory proteins of this sort.

The Hungarian workers have extracted from striated muscle still another protein, the N-protein. This substance is negatively birefringent and it has been localized in the I-bands, where it compensates for the positive birefringence of the prevailing lengths of the actomyosin filaments, consequently accounting for the relative isotropy of the I-band (129 to 133). Dempsey *et al.* (134), using cytochemical procedures, claim, however, to have found a negatively birefringent lipoidal material specially concentrated in the I-striations. At any rate, these results are in excellent harmony with certain observations and associated deductions derived from electron micrographic and x-ray studies of myosin, or actomyosin filaments in more or less intact muscle fibers (12, 121, 135, 136) i.e., that the filaments extend in a quite straight course through both A and I bands in both resting and contracted fibers, which indicates that there is no disorientation of material in the I bands such as had previously been postulated to account for the isotropy of these bands, and that shortening does not involve any visible coiling or folding of filaments. However, Jordan & Oster's light scattering studies (137) of actomyosin solutions indicate that this protein has the configuration of a slightly coiled particle and that ATP, presumably engendering a change comparable to contraction, increases the degree of coiling. Should these inferences prove to be valid, they will obviously be of greatest significance, for the coiling mechanism may correspond to the folding of α-myosin that Astbury (121) proposes for the behavior of the contractile substance in muscular contraction. Refer, however, to further discussion of the light scattering findings in the next section. It is noteworthy that electron microscope photographs (12, 134, 135) of fibers showing a denser packing of substance in the A bands proves that extra material is also localized here somewhat as the N-protein is localized in the I bands. Further detailed discussion of striational compartmentalization of strategic substances will be found in Barer's review (35).

Amberson *et al.* (138) report the partial extraction of myogen and myosin from whole unminced skeletal muscle after long soaking in appropriate media. This novel extraction procedure should give valuable information on the localization of substances in the

fiber when, as the authors plan, comparisons are made to the histological appearance of the extracted cells.

Although there is no doubt that both myosin and actin are present in muscle, there has been considerable uncertainty as to whether these proteins exist uncombined, in the resting fiber, or in the form of the actomyosin complex (118), and whether the actin is in the globular or fibrous state. Astbury (122, 139) now finds that the full x-ray diagram of muscle is effectively the sum of the diagrams given separately by extracted myosin and F-actin and hence concludes that the actomyosin complex prevails in muscle at rest. This result does establish the existence of F-actin in the muscle preparations that were used—and this is an important finding. But the reviewer, with some diffidence, questions the conclusion that the muscle diagram necessarily corresponds to the actomyosin complex. For it seems possible that a mixture of properly oriented but uncombined myosin and F-actin would also yield this x-ray pattern. Indeed, it might be expected that, if a true chemical combination between actin and myosin had taken place, the resultant x-ray diffractions would be different from the sum of those produced individually by these substances.

Of greatest importance for the comprehension of the binding forces responsible for the formation of the actomyosin complex is Bailey & Perry's demonstration (140) [see also (141, 142, 143)] that sulfhydryl groups of the myosin partner are involved in the process. Although many possibilities have been explored, no corresponding reactive group of the actin has as yet been disclosed, and it is therefore uncertain at present whether the results regarding the role of the myosin sulfhydryl groups indicate that a chemical combination occurs in actomyosin formation. [See (118) for further discussion of this point.]

The laboratory of Dubuisson has been very active in studying the electrophoresis of muscle proteins. Of particular interest is the complexity of the electrophoretic pattern which possibly indicates the presence of several muscle globulins [refer, however, to (124) for discussion of this view] and the change in this pattern due to fatigue or bromacetate rigor of the associated muscles (19, 144, 145). Confirming earlier results, Mrazek & Reed (146) have found that less myosin is extractable from fatigued than from rested frog and rat muscle. These various findings involving fatigue are significant in that they present additional proof of the contractile

role of myosin and suggest possible modifications in this protein due to activity.

Adenosinetriphosphatase activity.—In Meyerhof's laboratory a new, powerful adenosinetriphosphatase has been extracted from muscle (147, 148). In contrast to the older "Engelhardt" adenosinetriphosphatase, which is activated by calcium and inhibited by magnesium, has an optimum activity at about pH 9.0, and is identified by some workers with myosin, the new enzyme is activated by magnesium and inhibited by calcium, has a pH optimum around 7.4, and is completely separable from myosin. These results should serve to clarify the many conflicting reports concerning ionic activation and pH optima of adenosinetriphosphatase [see, e.g. (42) and (149)].

Of greater immediate significance is the application of these results to the claims (149, 150) that the adenosinetriphosphatase activity of myosin in muscle is far from sufficient to account for the phosphate released in contractile activity and that therefore ATP cannot be the immediate source of energy for the contractile system. But both these investigations deal with the calcium-activated and magnesium-inhibited adenosinetriphosphatase and therefore do not take into account the possible participation of the new Meyerhof magnesium-activated enzyme in the energization process. It is clear that the contribution of this adenosinetriphosphatase to the breakdown of ATP must now also be considered before drawing any conclusions concerning the energization of contraction by ATP. The assertion of the inadequacy of ATP as the energy source must, furthermore, be questioned since it is based on an analysis that does not take into consideration the great possibility that the activity of an adenosinetriphosphatase may be much greater in intact muscle than it is in purified extracts. Be that as it may, at least the energy-rich character of ATP has been further established, in a careful study (151) of the free energy of various phosphate bonds, in the finding that the pyrophosphate link yields 10,500 calories.

The question of the identity of the older adenosinetriphosphatase and myosin is still unsettled. Polis & Meyerhof (152), by special procedures, have obtained a myosin preparation with a threefold increase in adenosinetriphosphatase activity over the original myosin, thus indicating the separability of the myosin protein system from the enzyme. But Engelhardt (42), on various grounds, and Bailey (124, 125, 140), chiefly on the basis of the

parallel behavior of myosin and adenosinetriphosphatase under the action of agents that attack sulfhydryl-groups present strong evidence favoring the identification of the two.

Torda & Wolff (153) have shown that ACh in low concentrations increases, while *d*-tubocurarine, caffeine, and potassium in contracture producing concentrations decrease the adenosinetriphosphatase activity of myosin preparations. It is suggested that the ACh effect indicates that this substance may contribute to a more adequate recovery of muscle.

Effect of ATP on actomyosin sols.—One of the most interesting disclosures of the Hungarian workers is the great reduction in viscosity of actomyosin solutions caused by ATP (117, 118). This action has been interpreted as being due to the disaggregation of the original filamentous actomyosin into globular actin and myosin. Confirmation of this view seems to be afforded by the electron micrographic studies of Astbury *et al.* (154); addition of only 0.0013 *M* ATP transforms an initially highly anastomosed network of F-actomyosin fibers into a mass of distributed granular clumps. Furthermore, this study and that of Jakus & Hall (155), also using electron micrographic procedures, has apparently made visually evident the conclusions of the Hungarian school that actin is capable of a reversible fiber-globule transformation. But the theoretical interpretation of the light scattering experiments of Jordan & Oster (137) leads to the view that ATP does not dissociate actomyosin but increases its degree of coiling and thus transforms relatively long filaments into condensed granular particles, an inference in agreement with the view of the Needham school (156) which is based on viscometric and birefringence studies, but contrary to the conclusions drawn by Mommaerts (157) from light scattering and other studies. It is evident that further research is needed to settle this most important question—to decide whether ATP, in reducing the viscosity of actomyosin solutions, causes dissolution or coiling of the protein particles.

In another viscometric investigation, Mommaerts (158) shows that the effect of ATP on actomyosin is probably inhibited by magnesium and definitely activated by calcium and that each of these ions has effects on the recovery reversal of the ATP action opposite to that which it exerts on the initial reduction in viscosity. These ion effects suggest certain possible relations to the action of the same ions on the two adenosinetriphosphatases previously discussed. Mommaerts has also demonstrated that the ATP effect

occurs even when adenosinetriphosphatase activity has been inactivated by copper. In contradiction to this finding, however, stand the results of Bailey & Perry (140) that sulfhydryl reagents which inactivate the adenosinetriphosphatase activity cause parallel suppression of the ATP viscosity effect. Since these determinations have been obtained in a more detailed and extensive series of experiments, they would seem to have greater weight in the resolution of this problem. In any case, Bailey & Perry have interpreted their experiments in terms of the view that ATP disperses actomyosin and that this action results from the greater affinity of ATP for the enzyme centers of the myosin than is possessed by actin [see also (124)]. But the view of Jordan & Oster (137) that ATP induces only greater coiling of actomyosin evidently demands a reconsideration of this mechanism.

Effect of ATP on actomyosin gels; the Szent-Györgyi contractile system.—The revelation of the Szent-Györgyi school that undoubtedly impinges most forcefully on muscle physiology is the contraction of actomyosin gels in the presence of essentially physiological concentrations of ATP, potassium, and magnesium, and the reversal of this contraction, which also depends on ATP, and which ensues, e.g., upon increase in the concentration of potassium. This reversible process is demonstrable with actomyosin in suspension, or in the form of artificially spun threads, or as it exists in slices of striated muscle that have been thoroughly washed in distilled water (117, 118). Szent-Györgyi states (118): "This contraction of actomyosin . . . is the deepest impression of my research career. It means that this biological function, motion, has been reproduced with constituents of the body outside the living organism." Hence, he has put forward the view that the above actomyosin system, especially, it will be seen, as organized in the extracted muscle fibers, is in essence the isolated fundamental contractile mechanism of live muscle. In association with certain other observations, Szent-Györgyi has thus developed a theory of the contractile response. At least in certain circles, his proposals have received a very favorable reception.

We shall be concerned here almost exclusively with the contraction phenomenon of the actomyosin system. The relaxation behavior has not been so thoroughly investigated and, furthermore the requirements, e.g., that the potassium concentration must be increased to as high as 0.25 *M* for relaxation to occur seems to

exclude this as a possible physiological basis for relaxation. Yet it should be noted that striational compartmentalization of potassium, even in the living muscle fiber, might result in localized potassium concentrations of this order.

Szent-Györgyi makes clear that the contraction of actomyosin is in fact a synaeresis, and thus muscular contraction must involve a synaeresis. Astbury (121), however, notes that this colloidal behavior is very general and is characteristic of many colloids, e.g., swollen nylon. In the absence of precise knowledge of the nature of actual contraction, this may be a meaningless criticism, especially since Szent-Györgyi emphasizes that the phenomenon in actomyosin is very rapid and highly specific for ATP and is not obtained with either myosin or actin alone. Presumably, the rather unique synaeresis that is involved may be related to the specialized chemistry of myosin (121, 124, 159) and to the function of the sulfhydryl groups in the formation and behavior of actomyosin (140, 160). Probably the fact that sodium heparin alone, among many other drugs tested, almost completely inhibits the ATP contraction of the actomyosin thread (161) has some bearing on the problem. In any case, as Bailey states (120) "the urgent need before attempting to relate the actin-myosin-adenosinetriphosphate interrelationships to muscle contraction, is to resolve the mechanism of synearesis."

It is clear that the actomyosin thread formed from extracted myosin and actin cannot be considered as a model of the contractile system. Buchthal *et al.* (160) have shown, in essential confirmation of somewhat similar observations of Engelhardt (162, 163), that isotonically or isometrically loaded actomyosin threads lengthen or relax when treated with ATP, which is contrary to the shortening of freely floating threads, and that contracted threads have a reduced dynamic stiffness, which is contrary to the increased stiffness the Danish workers have measured in physiologically contracted single frog muscle fibers. Szent-Györgyi (118) correctly minimizes the importance of these results by emphasizing that the particles of the actomyosin thread are disoriented, while in muscle they are oriented. Moreover, in recent experiments he has shown (164) that the contractile substance, evidently oriented actomyosin, of the fibers of the rabbit *psoas* muscle that have been thoroughly extracted with water and 50 per cent glycerol contract when treated with ATP whether loaded or unloaded and they

"produce the same tension as in the intact muscle under the influence of maximal excitation." This is a most impressive demonstration and it strongly suggests on a purely phenomenological basis that the actomyosin system of these extracted dead fibers does behave as if it were the contractile system of muscle. Although the behavior of actomyosin gels in bulk or as artificially formed fibers has considerable interest, it is clear that the protein system of the extracted muscle fibers—be it oriented actomyosin, or some other related complex—must be taken as the Szent-Györgyi model of the contractile mechanism; and it is this system that will be critically studied.

Some serious difficulties are immediately raised on considering the observable effect of temperature on the actomyosin system. Varga (165) has shown that artificially spun actomyosin threads (with disoriented particles) and the actomyosin system of the dead fibers (with oriented particles) both contract, unloaded, as a logarithmic function of the temperature, there being no contraction at 0°C. and a maximal shortening at 16° to 18°C. It seems strange that both systems, despite the difference in orientation, should react similarly as a function of temperature. But more disturbing is the fact that the effect of temperature on the shortening of the extracted fibers is quite contrary to much experience with physiological muscular contraction. Innumerable myothermic experiments have been performed on live muscle at 0°C., and both extensive shortening and large tension development have been observed [see, e.g. (38, 166, 167)]. Furthermore, the author is not aware of any evidence indicating, at least for frog muscle, that physiological contraction is maximal at a critical temperature of about 16° to 18°C. Another important point of difference is found in the result of Heilbrunn and his students (65, 66) that the calcium ion, intracellularly introduced, practically specifically activates the protoplasmic clotting of isolated surviving single muscle fibers of the frog. It is beside the point that these authors attribute the clotting to a surface precipitation reaction and not to a synaeresis. The observable fact is that calcium, and not potassium or magnesium, initiates a kind of shortening of the live contractile system, and this is in contradiction to the contraction of Szent-Györgyi's extracted fiber model, which is activated by potassium and magnesium, and, in fact, can be inhibited by calcium. Incidentally, it is notable that again we meet with evidence, in systems which may somehow involve adenosinetriphosphatase activity, that

calcium and magnesium play opposite roles. It is therefore clear that the ion-involved contraction mechanisms in both the extracted and surviving muscle fibers should be studied in relation to the two different adenosinetriphosphatases previously discussed. At any rate, it seems, as Heilbrunn has for long stressed [e.g., see (65)], that more attention should be paid to the effect of various agents acting directly on living protoplasmic systems, and thus, in addition to his own experiments, those of Barer (41) dealing with the swelling of muscle fibers under the action of acids and alkalis are of great interest. However, the above direct phenomenological considerations lead us to conclude that, although the actomyosin system of the extracted fibers contracts in certain respects as does live muscle, it cannot be accepted as a representation of the physiological contractile system.

Even if this were not true, we would have strong doubts concerning the validity of the highly speculative mechanisms that have been advanced in explanation of the model's observable behavior. Szent-Györgyi makes much use of Varga's inferences (165) [see also (168)]: (*a*) that the actomyosin particles "either contract or not, but if they contract they contract maximally; contraction and relaxation are two distinct states of the contractile substance"; (*b*) that the transition of relaxed into contracted actomyosin increases with temperature and is, in general, a temperature-dependent allotropic equilibrium reaction with a calculable equilibrium constant, K; and (*c*) that, hence, the free energy of the transition can be determined from the relation, $\Delta F = -RT \ln K$. In Varga's studies, actual experiments were performed over the range from 0° to 16°C. and the free energy was found to be very small at 0°C. and to increase linearly with temperature. Furthermore, this linear relation was extrapolated to as high as 40°C., in view of the interest in this curve at higher temperatures, especially in connection with the behavior of mammalian muscle.

Now, there is no evidence at present from the x-ray data (121) that, in either actomyosin films or muscle, the particles of the contractile substance exist in the supposed distinct allotropic states of relaxation or contraction. However, what seems to be required to check this critically is a small-angle x-ray investigation of the relevant systems—a kind of study strongly recommended, moreover, on other grounds, by Schmitt *et al.* (12). We may more definitely question the validity of the equation for calculating the

free energy change: what is the meaning of the molar quantity of the substance that is involved, and what is the activity coefficient of the substance? And, what is the justification for the extrapolation of the free energy curve to higher temperatures, since the reported experiments extend only up to 16°C. and no evidence is presented of reversibility of the contraction-relaxation transformation in the extrapolated range? Furthermore, the very small free energy calculated for the low temperatures is clearly questionable, for, as previously intimated for shortening and tension development, contracting live muscles, at least of the frog, are capable in this range of large energy releases in the form of heat as well as mechanical output. It is true that Szent-Györgyi (118) has considered some of these questions, e.g., the molar weight problem; and the difficulty concerning reversibility may be resolved in part by the experiments on "contracture" (rigor?) of extracted frog and rabbit muscles studied at temperatures above 40°C. But, significant as these considerations may be, there still remains unresolved the great disparity between the small theoretically predicted free energy at low temperatures and the large energies actually released in comparable physiological contraction.

Still another feature of the theoretically derived energetics of the model is worth considering—the finding of Varga (165) that the transition from the relaxed to the contracted form of the actomyosin particles is endothermic with a heat of reaction of 56,000 calories. In so far as actual myothermic measurements are concerned, no such absorption of heat has ever been observed in the initial heat phase of a contraction. Indeed, as the latest work from Hill's laboratory demonstrates (76), an exothermic reaction is already proceeding at a high rate during the first few milliseconds following stimulation. Yet it must be admitted, as Szent-Györgyi states (117, 118), that we do not know what this initial contraction heat output represents; it might be true that the heat absorption of the endothermic reaction is masked by some concomitant exothermic change—a point also stressed by Bull (36, 169); and it is not excluded that the dip in rate of heat output between the contraction and relaxation phases of the initial heat may be attributed to some endothermic process. Be that as it may, it would be of interest to apply myothermic technique, if this is possible, to the study of the heat changes of Szent-Györgyi's extracted muscle fibers.

But, of greater interest in connection with Varga's endothermic reaction is the observation that, since the heat of reaction is 56,000 calories, and the free energy change (in both frog and rabbit extracted muscle, e.g., at 37°C.) is of the order of 7,000 to 8,000 calories, there must therefore be an accompanying large entropy change—of the order of 155 entropy units. Comparable entropy changes have been found in other biological systems, e.g., the reversible denaturation of trypsin (170) and of luciferase (171). Thus it is indicated that the free energy release of the model has its source mainly in an increase in entropy rather than a decrease in internal energy; and this raises the question as to whether muscle itself is an entropy or internal energy mechanism, a problem which is very closely related to another one—whether muscular contraction depends on a rubber-like or normal-body type elastic phenomenon. It is obvious that Szent-Györgyi's model, considered in terms of the endothermic nature of contraction, would be rubber-like; for the system absorbs heat when it contracts and releases heat when it lengthens, and thus its length changes depend essentially on entropy alterations.

The thermoelastic questions mentioned above are exceedingly complex and some of the attempts at solving them are of a highly controversial nature—as is made clear in admirable reviews by Guth (9) and by Fenn (172). For example, if the resting tension of a muscle fiber is, as Ramsey claims (7), solely a function of the sarcolemma, then there does not seem to be any sense in attempting to determine from stress-strain diagrams of such a fiber whether the inner tensionless contractile material has or has not rubber-like properties. It is evident that the source of the resting tension must be cleared up first. For active muscle, however, the problem is not so obscure. Since such muscle when stretched exhibits a cooling effect like a normal solid [see (172) for references], unlike the rise in temperature observed on stretching rubber-like materials, we must conclude that contracting muscle is not rubber-like. Bull (36, 169), however, has shown that the developed tension-length relation of single frog fibers in Ramsey's delta-state (7) does suggest rubber-like attributes and that the energy for contraction is entropic. But the delta-state is a highly abnormal condition of the contractile material and thus Bull's results can hardly apply to normal physiological responses.

Astbury (121), furthermore, develops a strong argument

against an entropy, and for an internal energy change in muscular contraction by reference to the high degree of chemical specificity characteristic of at least myosin: "the chains are studded with polar groups and the strong interactions between these, both within and between chains, are well removed from the behavior of hydrocarbons and such like." To bolster this line of thought may be added the fact that the SH group is specifically involved in the formation of actomyosin (140), and the possibility that highly specialized metabolic reactions, some of which are ionic, are concerned with contraction in muscle [e.g., see (9)]. In corroboration of Astbury's view it is notable that Woods[2] (173) [see also (121)] has shown by studying the effect of temperature on the tension of myosin films (and fibers of other keratins) that their elasticity is determined practically entirely by internal energy, and the entropy contribution may, in fact, be negative—results which are just contrary to the behavior of rubber. On the basis of the above evidence, we must conclude that the Szent-Györgyi model which contracts with a large entropy increase, and therefore is rubber-like, does not behave in accordance with either the contraction of live muscle or the mechanism responsible for generation of the elastic force of myosin as studied by Woods.

Quite apart from the bearing of this discussion of thermoelasticity on Szent-Györgyi's views, it should be noted that the above analysis indicates that any valid theory of contraction must involve an energization mechanism dependent on internal energy changes. This conclusion has relevance to another problem—the mechanism by which a stimulated muscle generates its tension. If the muscle were an entropy mechanism, then the development of its force would be a consequence of the heat motion of its contractile particles. But since this kind of energetic process seems to be excluded, the origin of the force must be sought elsewhere. The research of the Hungarian school offers no solution of this problem (unless it is to be found in the debatable synaeresis phenomenon previously discussed); but in this they are in the good company of all who have worked on the problem of muscular contraction, for it is a striking anomaly of current reasearch on muscle that, despite all that has been learned, essentially nothing is known about the process that generates force. The details of the mecha-

[2] Unfortunately, there is a typographical error in equation (2) of Wood's paper. The symbols for entropy, S, and force, K, must be interchanged. Needless to say, this has no bearing on the validity of the results obtained.

nism may, of course, be revealed by elucidating the nature of supercontraction of keratin fibers (121), which has been greatly advanced by the studies of Whewell & Woods (174) concerned with a copper-induced reversible supercontraction of wool fibers. The solution may also be found in an ionic exchange such as that which seems to be involved in the reversible shortening of calcium alginate fibers (175), or in the transverse bulging of ultrastructural units (71).

Another source of doubt in the validity of the extracted fiber model derives from a correlation of the controversy regarding activity versus recovery mechanochemical coupling with the view of Szent-Györgyi concerning the role of ATP in the mechanical response. We are concerned here with the question: does the coupling of ATP and its hydrolytic release of energy occur during the actuation of a contraction, i.e., during the latent and contraction periods (activity coupling), or during the recovery from contraction, i.e., during the relaxation period and maybe even later phases of the response (recovery coupling)? A considerable general literature has developed on this subject [e.g. (1, 7, 9, 13, 15 to 19, 36, 37, 42, 117, 118, 158, 169, 172, 176, 177)], but, notwithstanding the prevalence of a current vogue, so to speak, in favor of recovery coupling (1), the problem is far from settled.

Szent-Györgyi claims he has evidence that only contracted myosin has adenosinetriphosphatase activity (117, 118). Since ATP causes his actomyosin model to contract, he therefore proposes that ATP has three functions: (*a*) a trigger action by which very small amounts of ATP, too minute in themselves to release a contraction, can do so if there is already ATP absorbed on the contractile substance; (*b*) a contractile function by which the relatively large quantities of the adsorbed ATP permit the actomyosin to contract; and (*c*) an energy-donator action involving hydrolysis of ATP which occurs during the relaxation of the model. Thus, this conception of the role of ATP involves a combination of activity and recovery coupling; but, at any rate, the hydrolysis and energy release are associated with relaxation. Certain studies of the effect of ATP on actomyosin solutions, which include measurements of viscosity changes and associated adenosinetriphosphatase activity, are in general agreement with Szent-Györgyi's views [e.g. (156, 158)].

Now, it is not certain that only contracted myosin has adenosinetriphosphatase activity (119,120). But the real test of the above

conception of the role of ATP must be made in experiments on surviving muscle. Szent-Györgyi (118) believes that strong evidence in support of his views is found in the extensive series of experiments of Buchthal and co-workers [reviewed in (1)] in which ATP was squirted directly on living muscle fibers and the resultant responses recorded. But there is a critical difficulty in all these experiments—no decisive evidence is presented to prove that the noted contractile responses were due to the direct action of the applied ATP on the living contractile system. Indeed, Boyle & Conway (178) claim that the muscle fiber membrane is impermeable to ATP, although it should be noted that this is an inference derived from a study of the general ionic balance between the muscle cell and its external medium and that it does not depend on a direct investigation of ATP penetrability. Nevertheless, this inference is consistent with the prevailing conclusion that cells are not permeable to large ions, which is the form taken by the ATP in the solutions of Buchthal's experiments. However, the presence of action potentials after the application of ATP to isolated striated muscle fibers (179) rather clearly indicates that the immediate effect of the ATP was on the excitatory mechanism of the fibers and that the contractile responses followed in consequence of excitation. This view is bolstered by other findings of Buchthal *et al.* (180) showing that ATP has excitatory effects on anterior horn cells, and the result of Fischer & Fröhlicher (181) indicating that ATP can influence the function of the bundle of His, another purely excitatory tissue. It is evident that the Buchthal investigations of the release of contractions in single living fibers due to external application of ATP do not permit unequivocal conclusions as to the effect of ATP on the contractile system and therefore cannot be cited either to prove or disprove Szent-Györgyi's contentions. Clearly, very much needed are new experiments to determine the permeability of the muscle membrane to ATP and also investigations of the effect of intracellularly injected ATP on the contractile substance of muscle cells.

Unfortunately, certain other experiments concerned with the possible role of ATP in physiological contractions are also of rather uncertain interpretation. Dubuisson's studies (19, 182) of the pH alterations of activated muscle lead him to believe that ATP splits concurrently with contraction (activity coupling) and that creatine phosphate breakdown accompanies relaxation, but this

evidence though strongly indicative is nonetheless still indirect. The reviewer's studies of changes in the duration of the latent period caused by previous activity (183) or by pH variations (18) also only inferentially lead to the proposal of an activity coupling role for ATP; and his theory of mechanochemical coupling (18), although involving this inference, is not necessarily dependent on it in so far as the validity of the kinetics is concerned. The Fenn-effect has been cited as evidence for activity coupling, but Ramsey (7, 37) and Morales (184) believe that this effect is not inconsistent with recovery coupling. Finally, the parallel development of rigor and ATP depletion in activated iodoacetate muscles has been offered to prove the view that ATP is needed for relaxation (74, 75, 117, 118, 185); but, in such muscles, among still other changes, all the creatine phosphate, as well as the ATP, is irreversibly hydrolyzed and thus it might be inferred that this substance is required to cause relaxation, a view in accord with Dubuisson's claim (19) that creatine phosphate breakdown is associated with the relaxation phase in normal contraction.

There is one result of experiments on living muscle, however, that seems definitely to exclude the recovery coupling process—the observation that the relaxation initial heat in both isometric and isotonic contractions is due solely to dissipation of mechanical energy (of tension or of work) (13, 38, 172). Thus, evidently no exergonic chemical reaction accompanies relaxation. But there might be a thermoneutral reaction such as the dismutation of adenosinediphosphate by myokinase, or the resynthesis of ATP by interaction of either adenosinediphosphate or adenylic acid with creatine phosphate, these latter reactions being in accord with Dubuisson's inference that creatine phosphate breakdown is associated with relaxation. Quite apart from these speculations, the conclusion that the relaxation initial heat is not attributable to an exothermic chemical reaction is not consistent with the view that ATP is breaking down and releasing energy in a recovery coupling, especially since, in not only Szent-Györgyi's proposal for this kind of coupling [e.g. (118)], but in Binkley's as well (176) [see also (18)], the free energy of ATP hydrolysis is not completely utilized in recharging the contractile substance, and thus some of it should appear as heat, which, as indicated, is contrary to experience.

Thus, the available evidence regarding activity as against recovery coupling in live muscle does not all point unequivocally

in one direction. In the reviewer's opinion, however, the argument concerned with the explanation of the relaxation initial heat seems critically to exclude recovery coupling and favor activity coupling. It is to be hoped that the new Hill myothermic apparatus (76) will be applied to the further elucidation of this point. At any rate, there is no justification in Szent-Györgyi's references (117, 118) to research on live muscle, dealing with the general problem at issue, for him to conclude that the evidence definitely supports his theory of the detailed role of ATP in mechanochemical coupling; as indicated, the contrary may be true. However, one of the greatest needs in present muscle physiology is to obtain experimental results that can solve the problem of activity versus recovery coupling unambiguously, and such data will not only be useful for testing the validity of the Szent-Györgyi theory, but they will have the most fundamental general import as well.

Thus our general analysis of the Szent-Györgyi system proves on both phenomenological as well as speculative considerations based on present evidence that it is an inadequate model of the muscle's contractile system. Research on this problem, however, is very active and in great flux. It is not impossible that new results will lead to the need for a reconsideration of the above conclusion. It may be true, for example, that the observable limitations of the model that have been discussed can be explained by the fact that it exists apart from the excitatory system of the muscle fiber, which is destroyed by the extraction procedures used by Szent-Györgyi to prepare his isolated contractile system. In any case, at present, there still remains the bare mechanochemical fact that actomyosin does somehow contract when acted on by ATP in the presence of physiological concentrations not only of the ATP, but of the cations potassium and magnesium as well. It is therefore evident that the physiologist is faced with the stimulating task of correlating this striking behavior with the basic phenomena of actual contraction, and the biochemist, with elucidating the ultrastructural features of the system's mechanochemistry. It is at least in this sense that we must be greatly indebted to Szent-Györgyi and his co-workers for presenting us with these fascinating problems.

Miscellaneous

It is with regret that space limitations force the author to forego discussion of many important papers, which in most cases are

concerned with the more applied fields of muscle physiology. It should be of some use to the interested reader at least to put on record some pertinent references, dealing with a variety of topics, as follows: organization of motor units (186, 187, 188); electromyographic investigations of motor units (189, 190); kinesiology studied in the normal mammal mechanically (191 to 198), and electromyographically (199 to 203); electromyographic studies of speed of performance in relation to psychological behavior (204, 205); electromyography in various pathological states of the neuromuscular system (206 to 217); metabolic alterations during shock (218), in various muscular diseases (219), and in myocardial insufficiency (220); myasthenia gravis (221 to 225); muscular dystrophy (226 to 232); changes due to prolonged shortening (233); recuperation following tenotomy (234); and a significant group of papers on denervation atrophy concerned with histopathology (235 to 238), electromyography and related studies of fibrillation and fasciculation (239 to 244), chemical, endocrinological, and enzymological factors (245 to 251), electrodiagnosis (252 to 256), nerve and muscle fiber regeneration (257 to 262), and treatment (263 to 268). Also of interest are studies of: proprioceptor functions (28, 269, 270); ageing in respect to muscle chemistry (271, 272, 273) and chronaxie (274, 275); and, finally, the possible relation of a myotoxic factor in heat death (276, 277). The author hopes the next review in this series on muscle will give the attention to these contributions that they properly deserve.[3]

LITERATURE CITED

1. Buchthal, F., *Ann. Rev. Physiol.*, **9**, 119–48 (1947)
2. Eccles, J. C., *Ann. Rev. Physiol.*, **10**, 93–116 (1948)
3. Grundfest, H., *Ann. Rev. Physiol.*, **9**, 477–506 (1947)
4. Bremer, F., *Ann. Rev. Physiol.*, **9**, 457–76 (1947)
5. Wilbrandt, W., *Ann. Rev. Physiol.*, **9**, 581–604 (1947)
6. Teorell, T., *Ann. Rev. Physiol.*, **11**, 545–64 (1949)
7. Ramsey, R. W., *Ann. N. Y. Acad. Sci.*, **47**, 675–95 (1947)
8. Gilson, A. S., Jr., Schoepfle, G. M., and Walker, S. M., *Ann. N. Y. Acad. Sci.*, **47**, 697–714 (1947)
9. Guth, E., *Ann. N. Y. Acad. Sci.*, **47**, 715–66 (1947)
10. Kuffler, S. W., *Ann. N. Y. Acad. Sci.*, **47**, 767–79 (1947)
11. Fischer, E., *Ann. N. Y. Acad. Sci.*, **47**, 783–97 (1947)

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12. SCHMITT, F. O., BEAR, R. S., HALL, C. E., AND JAKUS, M. A., *Ann. N. Y. Acad. Sci.*, **47**, 799–812 (1947)
13. MEYERHOF, O., *Ann. N. Y. Acad. Sci.*, **47**, 815–34 (1947)
14. OCHOA, S., *Ann. N. Y. Acad. Sci.*, **47**, 835–48 (1947)
15. SANDOW, A., *Ann. N. Y. Acad. Sci.*, **47**, 667–72 (1947)
16. STEINBACH, H. B., *Ann. N. Y. Acad. Sci.*, **47**, 849–74 (1947)
17. SHEN, S. C., *Ann. N. Y. Acad. Sci.*, **47**, 875–94 (1947)
18. SANDOW, A., *Ann. N. Y. Acad. Sci.*, **47**, 895–929 (1947)
19. DUBUISSON, M., *Experientia*, **3**, 213–23 (1947)
20. SINGH, I., *Proc. Indian Acad. Sci.*, [B]**23**, 58–72 (1946)
21. BUCHTHAL, F., *Det. Kgl. Danske Videnskab. Selskab Biol. Med.*, **17**, 1–139 (1942)
22. BUCHTHAL, F., AND KNAPPEIS, G. G., *Acta Physiol. Scand.*, **6**, 123–48 (1943)
23. BUCHTHAL, F., KAISER, E., AND KNAPPEIS, G. G., *Acta Physiol. Scand.*, **8**, 16–37 (1944)
24. LUNDIN, G., *Acta Physiol. Scand.*, **7**, Suppl. 20 1–84 (1944)
25. HØNCKE, P., *Acta Physiol. Scand.*, **15**, Suppl. 48, 15, 1–230 (1947)
26. SANDOW, A., *J. Cellular Comp. Physiol.*, **24**, 221–56 (1944)
27. SCHOEPFLE, G. M., AND GILSON, A. S., JR., *J. Cellular Comp. Physiol.*, **26**, 119–30 (1945)
28. PERKINS, J. F., *Am. J. Physiol.*, **145**, 264–71 (1945)
29. MALCOLM, J. L., *J. Sci. Instruments*, **23**, 146–48 (1946)
30. ABBOTT, B. C., AND RITCHIE, J. M., *J. Physiol. (London)*, **107**, 5P (1948)
31. SANDOW, A., *Year Book Am. Phil. Soc.*, 182–85 (1944)
32. RALSTON, H. J., INMAN, V. T., STRAIT, L. A., AND SHAFFROTH, M. D., *Am. J. Physiol.*, **151**, 612–20 (1947)
33. SCHAEFER, H., AND GÖPFERT, H., *Arch. ges. Physiol. (Pflügers)*, **238**, 684–708 (1937)
34. GÖPFERT, H., AND SCHAEFER, H., *Arch. ges. Physiol. (Pflügers)*, **245**, 60–71 (1941)
35. BARER, R., *Biol. Revs. Cambridge Phil. Soc.*, **23**, 159–200 (1948)
36. BULL, H. B., *Quart. Bull. Northwestern Univ. Med. School*, **20**, 175–79 (1946)
37. RAMSEY, R. W., "Muscle Physics," *Medical Physics*, 784–98 (The Yearbook Publishers, Inc., Chicago, 1944)
38. HILL, A. V., *Proc. Roy. Soc. (London)* [B]**126**, 136–95 (1938)
39. SANDOW, A., *Federation Proc.*, **6**, 195 (1947)
40. SANDOW, A., *Federation Proc.*, **7**, 107–8 (1948)
41. BARER, R., *J. Anat.*, **81**, 259–85 (1947)
42. ENGELHARDT, V. A., *Advances in Enzymol.*, **6**, 147–91 (1946)
43. RALSTON, H. J., CLOSE, J. R., INMAN, V. T., AND FEINSTEIN, B., *Federation Proc.*, **7**, 97 (1948)
44. DERN, R. F., *Federation Proc.*, **6**, 96 (1947)
45. WALKER, S. M., *Am. J. Physiol.*, **149**, 7–23 (1947)
46. WALKER, S. M., *Am. J. Physiol.*, **150**, 451–60 (1947)
47. WALKER, S. M., *Federation Proc.*, **7**, 130 (1948)
48. WALKER, S. M., *Proc. Soc. Exptl. Biol. Med.*, **64**, 425–27 (1947)
49. WALKER, S. M., AND LAPORTE, Y., *J. Neurophysiol.*, **10**, 79–85 (1947)
50. RAMSEY, R. W., AND STREET, S. F., *Anat. Record, Suppl.*, **78**, 66 (1940)

51. GUTTMAN, S. A., HORTON, R. G., AND WILBER, D. T., *Am. J. Physiol.*, **119**, 463–73 (1937)
52. GRUMBACH, L., AND WILBER, D. T., *Am. J. Physiol.*, **130**, 433–44 (1940)
53. BROWN, G. L., BÜLBRING, E., AND BURNS, B. D., *J. Physiol.* (*London*), **107**, 115–28 (1948)
54. GOFFART, M., AND BROWN, G. L., *Compt. rend. soc. biol.*, **141**, 958–59 (1947)
55. GOFFART, M., *Compt. rend. soc. biol.*, **141**, 1278–79 (1947)
56. KOMETIANI, P. A., KLEIN, E. E., AND DOLIDZE, S. V., *Biokhimiya*, **11**, 253–62 (1946)
57. SCHEINER, H., *Compt. rend. soc. biol.*, **142**, 37–39 (1948)
58. TORDA, C., AND WOLFF, H. G., *J. Lab. Clin. Med.*, **31**, 650–53 (1946)
59. TORDA, C., AND WOLFF, H. G., *Am. J. Physiol.*, **146**, 567–72 (1946)
60. TORDA, C., AND WOLFF, H. G., *J. Lab. Clin. Med.*, **32**, 1374–77 (1947)
61. PETERFALVI, M., *Compt. rend. soc. biol.*, **141**, 1128–30 (1947)
62. AUBERT, X., AND DE LOOF, J., *Arch. intern. physiol.*, **55**, 307–9 (1948)
63. HOAGLAND, H., AND STONE, D., *Am. J. Physiol.*, **152**, 423–35 (1948)
64. TROWBRIDGE, C., AND JORDAN, J. R., *Am. J. Physiol.*, **148**, 222–28 (1947)
65. HEILBRUNN, L. V., AND WIERCINSKI, F. J., *J. Cellular Comp. Physiol.*, **29**, 15–32 (1947)
66. WOODWARD, A. A., JR., *J. Cellular Comp. Physiol.*, **31**, 359–94 (1948)
67. LAMBERT, E. H., MEDEROS, L. O., AND KELSEY, M. P., *Federation Proc.*, **7**, 68–69 (1948)
68. SANDOW, A., AND KARCZMAR, A. G., *Federation Proc.*, **4**, 62 (1945)
69. SANDOW, A., AND TURKEL, M., *Federation Proc.*, **4**, 62–63 (1945)
70. PEREIRA, J., JR., *Rev. brasil biol.*, **6**, 255–58 (1946); *Brit. Abstracts*, **AIII**, 557 (1947)
71. SCHOEPFLE, G. M., AND GILSON, A. S., JR., *J. Cellular Comp. Physiol.*, **27**, 105–14 (1946)
72. STEN-KNUDSEN, O., *Abstracts Intern. Physiol. Congr., 17th Congr. Oxford* (1947)
73. SANDOW, A., AND BRUST, M., *Proc. Soc. Exptl. Biol. Med.*, **63**, 462–64 (1946)
74. ERDÖS, T., *Studies Inst. Med. Chem. Univer. Szeged*, **3**, 51–56 (1943)
75. BATE-SMITH, E. C., AND BENDALL, J. R., *J. Physiol.* (*London*), **106**, 177–85 (1947)
76. ABBOTT, B. C., DOWNING, A. C., AND HILL, A. V., *J. Physiol.* (*London*), **106**, 31–32P (1947)
77. AUBERT, X., *Arch. intern. physiol.*, **55**, 348–61 (1948)
78. LEVIN, A., AND WYMAN, J., *Proc. Roy. Soc.* (*London*), [B]**101**, 218–43 (1927)
79. AUBERT, X., *Compt. rend. soc. biol.*, **140**, 571–73 (1946)
80. GUTTMAN, S. A., AND CATTELL, M., *Proc. Soc. Exptl. Biol. Med.*, **57**, 209–11 (1944)
81. BING, H. I., AND SKOUBY, A. P., *Acta Physiol. Scand.*, **14**, 80–85 (1947)
82. BARCROFT, H., AND MILLER, J. L. E., *J. Physiol.* (*London*), **106**, 13P (1947)
83. SHANES, A. M., *Science*, **107**, 679–81 (1948)
84. LING, G., *Federation Proc.*, **7**, 72–73 (1948)
85. HÖBER, R., *Physical Chemistry of Cells and Tissues*, Chap. 17, xiii and 676 pp. (The Blakiston Co., Philadelphia, 1945)
86. TOBIAS, J. M., *Federation Proc.*, **7**, 124, (1948)

87. BJURSTEDT, H., AND SCHMITERLÖW, C. G., *Acta Physiol. Scand.*, **6**, 359–67 (1943)
88. JACOB, J., *Arch. intern. physiol.*, **52**, 417–38 (1942)
89. DE MEYER, J., *Arch. intern. physiol.*, **16**, 44–57, 64–99, 172–92, 193–227 (1921)
90. SICHEL, F. J., AND PARKHURST, C., *Federation Proc.*, **6**, 201 (1947)
91. SICHEL, F. J., AND PARKHURST, C., *Federation Proc.*, **7**, 115–16 (1948)
92. IVANOFF, N., AND SCHEINER, H., *Compt. rend. soc. biol.*, **140**, 250–52 (1946)
93. KATZ, B., AND LOU, C. H., *J. Physiol. (London)*, **106**, 30–31P (1947)
94. SOLLMAN, T., *Am. J. Physiol.*, **148**, 299–301 (1947)
95. SIMONSON, E., OMACHI, A., AND VISSCHER, M. B., *Proc. Soc. Exptl. Biol. Med.*, **61**, 91–92 (1946)
96. BOCK, H., *Arch. ges. Physiol. (Pflügers)*, **249**, 301–7 (1947)
97. BOURGUIGNON, G., AND HUMBERT, R., *Compt. rend. soc. biol.*, **141**, 549–51 (1947)
98. JAQUES, S., *Rev. can. biol.*, **5**, 511–47 (1946)
99. SZEPSENWOL, J., *Anat. Record.*, **95**, 125–46 (1946)
100. SZEPSENWOL, J., *Anat. Record.*, **98**, 67–85 (1947)
101. BOZLER, E., *Am. J. Physiol.*, **149**, 299–301 (1947)
102. EYSTER, J. A. E., AND GILSON, W. E., *Am. J. Physiol.*, **150**, 572–79 (1947)
103. KATZ, B., AND LOU, C. H., *J. Physiol. (London)*, **106**, 29P (1947)
104. KATZ, B., AND LOU, C. H., *J. Physiol. (London)*, **106**, 30P (1947)
105. BULLOCK, T. H., GRUNDFEST, H., NACHMANSOHN, D., AND ROTHENBERG, M. A., *J. Neurophysiol.*, **10**, 11–21 (1947)
106. NACHMANSOHN, D., BERMAN, M., AND WEISS, M., *J. Biol. Chem.*, **16**, 295–96 (1947)
107. KROP, S., *Federation Proc.*, **6**, 347 (1947)
108. FINERTY, J. C., *Am. J. Physiol.*, **151**, 107–9 (1947)
109. SCHEINER, H., *Compt. rend. soc. biol.*, **140**, 37–40 (1946)
110. SCHEINER, H., *Compt. rend. soc. biol.*, **140**, 113–15 (1946)
111. SCHEINER, H., *Compt. rend. soc. biol.*, **142**, 40–42 (1948)
112. SCHEINFINKEL, N., *Helv. Physiol. et Pharmacol. Acta*, **4**, 83–103 (1946)
113. SCHEINFINKEL, N., *Helv. Physiol. et Pharmacol. Acta*, **4**, C53–54 (1946)
114. KUFFLER, S. W., *J. Neurophysiol.*, **9**, 367–77 (1946)
115. ZAWADSKI, B., *Polski Tygodnik Lekarski*, **1**, 1454–55 (1946)
116. BISHOP, G. H., AND GILSON, A. S., JR., *Am. J. Physiol.*, **82**, 478–95 (1927)
117. SZENT-GYÖRGYI, A., *Chemistry of Muscular Contraction*, iv and 150 pp. (Academic Press Inc., New York, 1947)
118. SZENT-GYÖRGYI, A., *Nature of Life—A Study on Muscle*, 91 pp. (Academic Press Inc., New York, 1948)
119. MEYERHOF, O., *Arch. Biochem.*, **15**, 166–68 (1947)
120. BAILEY, K., *Nature*, **160**, 550 (1947)
121. ASTBURY, W. T., *Proc. Roy. Soc. (London)* [B]**134**, 303–28 (1947)
122. ASTBURY, W. T., Paper presented at 6th Intern. Congr. Exptl. Cytology, Stockholm, Sweden, 1947
123. ASTBURY, W. T., *J. chim. phys.*, **44**, 3–8 (1947)
124. BAILEY, K., *Ann. Repts on Progress Chem. (Chem. Soc. London)*, **43**, 280–87 (1947)
125. BAILEY, K., *J. Soc. Leather Trade Chemists*, **32**, 18–24 (1948)

126. SCHMITT, F. O., AND DENUES, A. R. T., *Annual Rev. Physiol.*, **10**, 1–16 (1948)
127. BANGA, I., GUBA, F., AND SZENT-GYÖRGYI, A., *Nature*, **159**, 194 (1947)
128. KALCKAR, H. M., *J. Biol. Chem.*, **153**, 355–67 (1944)
129. MATOLTSY, A. G., AND GERENDÁS, M., *Nature*, **159**, 502–3 (1947)
130. MATOLTSY, A. G., AND GERENDÁS, M., *Hung. Acta Physiol.*, **1**, 116–20 (1948)
131. GERENDÁS, M., SZARVOS, P., AND MATOLTSY, A. G., *Hung. Acta Physiol.*, **1**, 121–23 (1948)
132. GERENDÁS, M., MATOLTSY, A. G., *Hung. Acta Physiol.*, **1**, 124–27 (1948)
133. GERENDÁS, M., AND MATOLTSY, A. G., *Hung. Acta Physiol.*, **1**, 128–33 (1948)
134. DEMPSEY, E. W., WISLOCKI, G. B., AND SINGER, M., *Anat. Record*, **96**, 221–48 (1946)
135. HALL, C. E., JAKUS, M. A., AND SCHMITT, F. O., *Biol. Bull.*, **90**, 32–50 (1946)
136. REED, R., AND RUDALL, K. M., *Biochem. et Biophys. Acta*, **2**, 19–26 (1948)
137. JORDAN, W. K., AND OSTER, G., *Science*, **108**, 188–90 (1948)
138. AMBERSON, W. R., ANDERSON, R. S., CHINN, B., AND ERDÖS, T., *Federation Proc.*, **7**, 2 (1948)
139. ASTBURY, W. T., *Nature*, **160**, 388 (1947)
140. BAILEY, K., AND PERRY, S. V., *Biochem. et Biophys. Acta*, **1**, 506–16 (1947)
141. GODEAUX, J., *Comp . rend. soc. biol.*, **140**, 675–78 (1946)
142. GODEAUX, J., *Compt. rend. soc. biol.*, **140**, 678–80 (1946)
143. FISCHER, P., AND GOFFART, M., *Compt. rend. soc. biol.*, **141**, 527–28 (1947)
144. JACOB, J., *Experientia*, **3**, 241–43 (1947)
145. DUBUISSON, M., AND PEZEU, M. H., *Compt. rend. soc. biol.*, **141**, 800–2 (1947)
146. MRAZEK, R. G., AND REED, C. I., *Am. J. Physiol.*, **149**, 177–79 (1947)
147. KIELLEY, W. W., AND MEYERHOF, O., *J. Biol. Chem.*, **174**, 387–88 (1948)
148. KIELLEY, W. W., *Federation Proc.*, **7**, 164 (1948)
149. BRAVERMAN, I., AND MORGULIS, S., *J. Gen. Physiol.*, **31**, 411–15 (1948)
150. MOMMAERTS, W. F. H. M., AND SERAIDARIAN, K., *J. Gen. Physiol.*, **30**, 401–22 (1948)
151. MEYERHOF, O., AND OESPER, P., *Federation Proc.*, **7**, 174 (1948)
152. POLIS, B. D., AND MEYERHOF, O., *J. Biol. Chem.*, **169**, 389–401 (1947)
153. TORDA, C., AND WOLFF, H. G., *Am. J. Physiol.*, **152**, 86–92 (1948)
154. ASTBURY, W. T., PERRY, S. V., REED, R., AND SPARK, L. C., *Biochim. et Biophys. Acta*, **1**, 379–92 (1947)
155. JAKUS, M. A., AND HALL, C. E., *J. Biol. Chem.*, **167**, 705–14 (1947)
156. DAINTY, M., KLEINZELLER, A., LAWRENCE, A. S. C., MIALL, M., NEEDHAM, J., NEEDHAM, D. M., AND SHEN, S. C., *J. Gen. Physiol.*, **27**, 355–99 (1944)
157. MOMMAERTS, W. F. H. M., *Arkiv Kemi Mineral. Geol.*, [A]**19**, 1–11 (1945)
158. MOMMAERTS, W. F. H. M., *J. Gen. Physiol.*, **31**, 361–75 (1948)
159. BAILEY, K., *Advances in Protein Chem.*, **1**, 289–317 (1944)
160. BUCHTHAL, F., DEUTSCH, A., KNAPPEIS, G. G., AND PETERSEN, A., *Acta Physiol. Scand.*, **13**, 167–180 (1947)
161. MCINTYRE, A. R., AND BRAVERMAN, I., *Federation Proc.*, **6**, 158 (1947)
162. ENGELHARDT, V. A., LYUBIMOVA, M. N., AND MEITINA, R. A., *Compt. rend. acad. sci. U.R.S.S.*, **30**, 644–46 (1941); *Chem. Abstracts*, **37**, 391–92 (1943)
163. ENGELHARDT, V. A., *Yale J. Biol. and Med.*, **15**, 21–38 (1942)
164. SZENT-GYÖRGYI, A. (Personal communications, August 19 and August 25, 1948)

165. VARGA, L., *Hung. Acta Physiol.*, **1**, 1–8 (1946)
166. DOI, Y., *J. Physiol.* (*London*), **54**, 218–26, 335–41 (1920)
167. HILL, A. V., *Adventures in Biophysics*, ix and 162 pp. (University of Pennsylvania Press, Philadelphia, 1931)
168. VARGA, L., *Hung. Acta Physiol.*, **1**, 138–41 (1948)
169. BULL, H. B., *J. Am. Chem. Soc.*, **67**, 2047–48 (1945)
170. ANSON, M. L., AND MIRSKY, A. E., *J. Gen. Physiol.*, **17**, 393–98 (1934)
171. EYRING, H., AND MAGEE, J. L., *J. Cellular Comp. Physiol.*, **20**, 169–77 (1942)
172. FENN, W. O., in R. Höber's, *Physical Chemistry of Cells and Tissues*, xiii and 676 pp. (The Blakiston Co., Philadelphia, 1945)
173. WOODS, H. J., *J. Colloid Sci.*, **1**, 407–19 (1946)
174. WHEWELL, C. S., AND WOODS, H. J., *Proc. Symposium Fibrous Proteins; Soc. Dyers Colourists*, 50–57 (1946)
175. MONGAR, J. L., AND WASSERMAN, A., *J. Physiol.* (*London*), **106**, 32P (1947)
176. BINKLEY, F., *Science*, **102**, 477–79 (1945)
177. SANDOW, A., *Trans. N. Y. Acad. Sci.*, [2]**7**, 139–51 (1945)
178. BOYLE, P. J., AND CONWAY, E. J., *J. Physiol.* (*London*), **100**, 1–63 (1941)
179. BUCHTHAL, F., DEUTSCH, A., AND KNAPPEIS, G. G., *Acta Physiol. Scand.*, **8**, 271–87 (1944)
180. BUCHTHAL, F., ENGBAEK, L., STEN-KNUDSEN, O., AND THOMASEN, E., *J. Physiol.* (*London*), **106**, 3P (1947)
181. FISCHER, H., AND FRÖHLICHER, R., *Experientia*, **4**, 155–56 (1948)
182. DUBUISSON, M., *J. Physiol.* (*London*), **94**, 461–82 (1939)
183. SANDOW, A., *Ann. N. Y. Acad. Sci.*, **46**, 153–84 (1946)
184. MORALES, M. (Personal communication, October 16, 1947)
185. KALCKAR, H. M., *Chem. Revs.*, **28**, 71–178 (1941)
186. MARKEE, J. E., THOMPSON, W. W., AND THORNE, S. O., JR., *Anat. Record*, **97**, 355 (1947)
187. VAN HARREVELD, A., *Arch. néerland. physiol.*, **28**, 408–12 (1946)
188. VAN HARREVELD, A., *Am. J. Physiol.*, **151**, 96–106 (1947)
189. DENSLOW, J. S., *J. Neurophysiol.*, **11**, 209–15 (1948)
190. DENSLOW, J. S., AND GRAHAM-SERVICE, D. M., *Federation Proc.*, **7**, 27–28 (1948)
191. DUVALL, E. N., HOUTZ, S. J., AND HELLEBRANDT, F. A., *Arch. Phys. Med.*, **28**, 213–18 (1947)
192. ELKINS, E. C., AND WAKIM, K. G., *Arch. Phys. Med.*, **28**, 555–68 (1947)
193. FISCHER, E., *Arch. Phys. Med.*, **28**, 295–300 (1947)
194. HALL, V. E., MUÑOZ, E., AND FITCH, B., *Arch. Phys. Med.*, **28**, 493–99 (1947)
195. HAXTON, H. A., *Anat. Record*, **98**, 337–46 (1947)
196. HUGH-JONES, P., *J. Physiol.* (*London*), **105**, 332–44 (1947)
197. REZENFELD, I. H., GERARD, R. W., BOYARSKY, L. H., AND SMYTH, J. B., *Federation Proc.*, **6**, 194 (1947)
198. WEDDELL, G., *Ann. Rheumatic Diseases*, **6**, 189–91 (1947)
199. BIERMAN, W., AND YAMSHON, L. J., *Arch. Phys. Med.*, **29**, 206–11 (1948)
200. DEMPSTER, W. T., AND FINERTY, J. C., *Am. J. Physiol.*, **150**, 596–606 (1947)
201. GELLHORN, E., *Arch. Phys. Med.*, **28**, 568–74 (1947)
202. LOOFBOUROW, G. N., *J. Neurophysiol.*, **11**, 153–67 (1948)
203. MORTENSEN, O. A., SULLIVAN, W. E., AND MILES, M., *Anat. Record*, **97**, 422 (1947)

204. SHAW, W. A., AND KLINE, L. H., *J. Exptl. Psychol.*, **37**, 146–58 (1947)
205. KENNEDY, J. L., AND TRAVIS, R. C., *Science*, **105**, 410–11 (1947)
206. BOWDEN, R. E. M., *Proc. Roy. Soc. Med.*, **39**, 339–41 (1946)
207. BRAZIER, M. A. B., WATKINS, A. L., AND MICHELSEN, J. J., *Arch. Neurol. Psychiat.*, **56**, 651–58 (1946)
208. PERDRUP, A., *Acta Pharmacol. Toxicol.*, **2**, 121–37 (1946)
209. WEDDELL, G., *Proc. Roy. Soc. Med.*, **39**, 339 (1946)
210. JASPER, H. H., *Federation Proc.*, **6**, 137–38 (1947)
211. KUGELBERG, E., *J. Neurol. Neurosurg. Psychiat.*, **10**, 122–33 (1947)
212. TURPIN, R., LEFEBVRE, J., LAROCHE, C., AND LERIQUE, J., *Compt. rend. soc. biol.*, **141**, 164–65 (1947)
213. WIERSMA, C. A. G., *Proc. Soc. Exptl. Biol. Med.*, **61**, 85–89 (1946)
214. HODES, R., *Federation Proc.*, **6**, 130–31 (1947)
215. HODES, R., *Am. J. Med. Sci.*, **213**, 509–10 (1947)
216. HODES, R., *Federation Proc.*, **7**, 56 (1948)
217. HUDDLESTON, O. L., AND GOLSETH, J. G., *Arch. Phys. Med.*, **29**, 92–98 (1948)
218. LE PAGE, G. A., *Am. J. Physiol.*, **146**, 267–81 (1946)
219. HOAGLAND, C., *Advances in Enzymol.*, **8**, 193–230 (1946)
220. MANGUN, G. H., AND MYERS, V. C., *Arch. Internal Med.*, **78**, 441–46 (1946)
221. PIETRI, R., *N. Y. State J. Med.*, **44**, 1575–77 (1944)
222. COMROE, J. H., Jr., TODD, J., GAMMON, G. D., LEOPOLD, I. H., KOELLE, G. B., BODANSKY, O., AND GILMAN, A., *Am. J. Med. Sci.*, **212**, 641–51 (1946)
223. TORDA, C., AND WOLFF, H. G., *Federation Proc.*, **6**, 216 (1947)
224. GADDUM, J. H., AND WILSON, A., *Nature*, **159**, 680–81 (1947)
225. RUDD, J. L., AND CULLINAN, J. F., *Arch. Phys. Med.*, **29**, 354–57 (1948)
226. HAFNER, P. G., ANDERSON, R., DAVIS, H., CHUINARD, E. G., *Northwest Med*, **45**, 256–58 (1946)
227. HOAGLAND, C., *Currents in Biochemical Research*, Chap. 26, viii and 486 pp. (Interscience Publishers, New York, 1946)
228. MARTIN, G. J., *Exptl. Med. and Surg.*, **4**, 326–32 (1946)
229. SANDIFER, P. H., *J. Neurol. Neurosurg. Psychiat.*, **9**, 81–83 (1946)
230. HOVE, E. L., AND HARRIS, P. L., *J. Nutrition*, **33**, 95–106 (1947)
231. HUMMEL, J. P., *Federation Proc.*, **6**, 263–64 (1947)
232. MILHORAT, A. T., *Federation Proc.*, **7**, 80–81 (1948)
233. HAJEK, N. M., GODBEY, M. E., AND HINES, H. M., *Arch. Phys. Med.*, **28**, 690–95 (1947)
234. THOMSEN, P., AND LUCO, J. V., *Proc. Soc. Exptl. Biol. Med.*, **60**, 381–82 (1945)
235. ALTSCHUL, R., *Science*, **103**, 566–67 (1946)
236. BETZ, H., *Compt. rend. soc. biol.*, **141**, 1274–76 (1947)
237. BETZ, H., *Compt. rend. soc. biol.*, **141**, 1276–78 (1947)
238. CAREY, E. J., HAUSHALTER, E., MASSOPUST, L. C., GAROFALO, F., LYNCH, J., TALBOT, D., AND SOCOLOFF, E., *Proc. Soc. Exptl. Biol. Med.*, **64**, 192–200 (1947)
239. FORSTER, F. M., BORKOWSKI, W. J., AND ALPERS, B. J., *Arch. Neurol. Psychiat.*, **56**, 276–83 (1946)
240. ALPERS, B. J., BERRY, R. G., AND FORSTER, F. M., *Federation Proc.*, **6**, 69 (1947)
241. GOLSETH, J. G., AND FIZZELL, J. A., *Am. J. Physiol.*, **150**, 558–67 (1947)
242. KIRCHHOF, J. K. J., *Nervenarzt*, **18**, 50–55 (1947)

243. MEAD, S., *Arch. Phys. Med.*, **28,** 93–99 (1947)
244. WEDDELL, G., *Brit. J. Phys. Med.*, **10,** 53–54 (1947)
245. DIAZ-GUERRERO, R., THOMSON, J. D., AND HINES, H. M., *Am. J. Physiol.*, **151,** 91–95 (1947)
246. FISCHER, E., HUF, E., RAMSEY, V. W., AND RYLAND, C. R., *Federation Proc.*, **6,** 103 (1947)
247. SCHAPIRA, G., AND DREYFUS, J. C., *Compt. rend. soc. biol.*, **141,** 155–57 (1947)
248. DREYFUS, J. C., AND SCHAPIRA, G., *Compt. rend. soc. biol.*, **141,** 157–59 (1947)
249. FISCHER, E., *Arch. Phys. Med.*, **29,** 291–300 (1948)
250. HUFF, E. G., *Federation Proc.*, **7,** 59 (1948)
251. MARTIN, A. W., AND SOLA, O. M., *Federation Proc.*, **7,** 78 (1948)
252. BONNERDEL, R., *Rev. can. biol.*, **5,** 87–118 (1946)
253. POLLOCK, L. J., GOLSETH, J. G., AND ARIEFF, A. J., *Research Pubs. A soc. Research Nervous Mental Disease*, **25,** 236–57 (1946)
254. GOLSETH, J. G., AND FIZZELL, J. A., *Arch. Phys. Med.*, **28,** 757–63 (1947)
255. POLLOCK, L. J., GOLSETH, J. G., AND ARIEFF, A. J., *Surg. Gynecol. Obstet.*, **84,** 1077–82 (1947)
256. WARIDEL, A., AND FLEISCH, A. F., *Helv. Physiol. et Pharmacol. Acta*, **5,** 63 (1947)
257. WEISS, P., AND HOAG, A., *J. Neurophysiol.*, **9,** 413–18 (1946)
258. JASPER, H. H., *Trans. Roy. Soc. Canada* [V] **40,** 81–92 (1946)
259. CLARK, W. E. L., AND WAJDA, H. S., *J. Anat.*, **81,** 59–63 (1947)
260. POLLOCK, L. J., GOLSETH, J. G., MAYFIELD, F., ARIEFF, A. J., LIEBERT, E., AND OESTER, Y. T., *J. Am. Med. Assoc.*, **134,** 330–33 (1947)
261. VAN HARREVELD, A., *Am. J. Physiol.*, **150,** 670–76 (1947)
262. GUTMAN, E., *J. Neurophysiol.*, **11,** 279–94 (1948)
263. KOSMAN, A. J., OSBORNE, S. L., AND IVY, A. C., *Am. J. Physiol.*, **145,** 447–51 (1946)
264. SUSKIND, M. I., HAJEK, N. M., AND HINES, H. M., *Arch. Phys. Med.*, **27,** 133–35 (1946)
265. HAJEK, N. M., AND HINES, H. M., *Federation Proc.*, **6,** 119 (1947)
266. KOSMAN, A. J., OSBORNE, S. L., AND IVY, A. C., *Arch. Phys. Med.*, **28,** 12–17 (1947)
267. KOSMAN, A. J., OSBORNE, S. L., AND IVY, A. C., *Arch. Phys. Med.*, **28,** 7–12 (1947)
268. SMART, M., *Arch. Phys. Med.*, **28,** 429–38 (1947)
269. KORR, I. M., *J. Am. Osteopath. Assoc.*, **47,** 191–98 (1947)
270. DENSLOW, J. S., KORR, I. M., AND KREMS, A. D., *Am. J. Physiol.*, **150,** 229–38 (1947)
271. BOY, G., AND CHEYMOL, J., *Bull. soc. chim. biol.*, **27,** 105–11 (1945)
272. HORVATH, S. M., *Am. J. Physiol.*, **145,** 77–92 (1945)
273. HORVATH, S. M., *J. Gerontol.*, Pt. 1, **1,** 213–21 (1946)
274. BOY, G., CHEYMOL, J., AND PELOU, A., *Bull. soc. chim. biol.*, **28,** 126–30 (1946)
275. BOURGUIGNON, G., AND BOURLIÈRE, F., *Compt. rend. soc. biol.*, **141,** 596–97 (1947)
276. HEILBRUNN, L. V., HARRIS, D. L., LE FEVRE, P. G., WILSON, W. L., AND WOODWARD, A. A., *Physiol. Zoöl.*, **19,** 404–29 (1946)
277. HIESTAND, W. A., AND FULLER, F. D., *Federation Proc.*, **7,** 54–55 (1948)

HEMATOPOIESIS[1]

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Erythropoiesis

Porphyrin metabolism.—Reviews: Chemistry (1 to 4); protoporphyrin (5); coproporphyrin (6); metalloporphyrins (7). Technical papers (8, 9).

Knowledge of the biosynthesis of protoporphyrin has recently been considerably extended through the use of isotopes. Former theories concerning the synthesis of protoporphyrin from preformed pyrrole rings such as proline, hydroxyproline, and tryptophane have had to be discarded. It has now been demonstrated that the nitrogen (10) and the alpha carbon of glycine (11) are utilized in the *in vivo* synthesis of protoporphyrin. Grinstein, Kamen & Moore (12) have shown that the carboxyl carbon of glycine is not utilized in the biosynthesis of protoporphyrin but is incorporated into the globin molecule. Shemin, London & Rittenberg (13, 14) have observed the *in vitro* synthesis of heme from glycine in the nucleated red cells of the duck and in human red cells from cases of sickle cell anemia.

Thus it can be concluded that the alpha carbon and amino nitrogen of glycine participate in the formation of the pyrrole ring. Since the carboxyl carbon does not participate it is unlikely that the ring is formed by a condensation of glycine with a β-ketoaldehyde as previously postulated (10, 15). Acetate (16) participates in the formation of some of the side chains of heme. Proline, glutamic acid, leucine, and ammonia participate only indirectly by enriching the body nitrogen from which the precursors of heme are synthesized. It may be anticipated that as the isotope studies are extended valuable knowledge of the intermediary steps will be gained.

In the biological synthesis of heme the following two possibili-

[1] Because of limitations of space only certain aspects of the formation of the cellular elements of the blood will be discussed here. The subjects of leukopoiesis and thrombocytopoiesis have had to be omitted completely. For the sake of orientation and clarity it has been found desirable in a few instances to cite publications which appeared prior to the period covered, namely July, 1947 to June, 1948, inclusive.

ties must be considered: the porphyrin ring is formed around the iron, or the iron is inserted into the previously formed porphyrin ring. Granick & Gilder (17, 18) using *Haemophilus influenzae* have presented evidence that the porphyrin ring is first synthesized and the iron is then inserted. Further support for this hypothesis is found in the fact that free protoporphyrin has been detected in red blood cells in small amounts by many observers (19). Granick (5) has suggested that the methyl groups of protoporphyrin protect the molecule from any possible side reactions in the cell, the vinyl groups are necessary for the insertion of iron into the porphyrin ring, and the two ionized propionic acid side chains bind the two strongly basic groups of the globin. He further postulates that the third attachment of the heme to the globin is through the iron to a specific group on the protein, possibly an imidazole nitrogen. This last attachment, representing the fifth coordination link, may perhaps be responsible for maintaining the iron in the ferrous state and may endow the heme with the peculiar property whereby the sixth coordination link can be reversibly held by an oxygen molecule. In this very excellent paper other aspects of the internal structure of hemoglobin are very ably discussed.

A relation between pteroylglutamic acid and the synthesis of the porphyrin portion of metal-porphyrin enzymes has been suggested by Totter and co-workers (20, 21). They have found that potassium cyanide, caffeine, or hydrogen peroxide, when added to cultures of *Streptococcus faecalis* or *Corynebacterium hoffmannii*, inhibits growth and porphyrin production. These effects are partially reversed by pteroylglutamic acid. Furthermore, urine collected from patients with pernicious anemia two hours after treatment with pteroylglutamic acid was found to contain relatively large quantities of an unidentified porphyrin (22).

Cartwright & Wintrobe (23) have observed that swine deficient in pyridoxine develop a significant lowering in the amount of free protoporphyrin in the erythrocytes early in the course of the deficiency. They have suggested that the fundamental disturbance in erythropoiesis in pyridoxine deficiency may be a failure to synthesize protoporphyrin.

Grinstein, Silva & Wintrobe (24) have studied free erythrocyte protoporphyrin (EP) in a variety of experimental conditions and have concluded that an increase usually signifies uncompleted hemoglobin synthesis as a result of very rapid erythropoiesis with

liberation of immature cells, or due to iron deficiency or toxic factors. However, since the EP was significantly higher in venous blood obtained from the spleen following stasis they further concluded that a rise in EP may also be a result of intracellular hemoglobin degradation. Studies in the same laboratory on EP in a large group of normal and anemic subjects have been reported by Cartwright *et al.* (25). In general, it was found that there was usually an increase in EP in anemic states associated with a normoblastic bone marrow due to a disturbance in hemoglobin synthesis, i.e., iron deficiency, anemia of infection, nephritis, lead poisoning, and some cases of "lymphoma" and leukemia. In contrast, in pernicious anemia, which is characterized by a megaloblastic bone marrow, there was no increase in the protoporphyrin content of the erythrocytes.

Vitamin B_{12}.—The isolation of a crystalline compound from liver which in microgram quantities produces positive hematologic responses in patients with pernicious anemia has been announced by the chemists of the Merck Laboratories (26). This discovery was facilitated by the observation of Shorb (27, 28) that highly active antipernicious anemia liver extracts stimulate the growth of *Lactobacillus lactis* Dorner and that their microbiological activity paralleled their clinical activity. This new vitamin was reported by West (29) to be active in three patients with pernicious anemia following single intramuscular injections of as little as 3, 6, and 15 μg., respectively. Spies and co-workers (30, 31) have administered similarly small amounts to each of two patients with nutritional macrocytic anemia, pernicious anemia, and tropical sprue, and to a single patient with nontropical sprue and have observed a reticulocytosis in each instance. Details concerning the chemical nature of this substance have not yet been reported, nor is it yet known whether this compound contains the agent in liver extract which prevents neural degeneration in pernicious anemia. Since 1 μg. of the vitamin is approximately equivalent to 1 U.S.P. unit, and since the clinical potency of the refined liver extracts parallels the *Lactobacillus lactis* Dorner (LLD) assay activity it seems likely that the new vitamin may be the long searched for antipernicious anemia factor or a part of it.

Smith (32), in England, simultaneously reported the isolation from five tons of beef liver of two highly purified red pigments which are active in pernicious anemia when given in amounts of

about 20 μg. daily. In three patients with subacute combined degeneration of the cord the material is reported to have been effective but details are not given. Diffusion studies indicate the molecular weight of each of the pigments to be about 3000.

Pteroylglutamic acid, pernicious anemia, and related macrocytic anemias.—Several reviews have been published which deal with the chemistry of the pteridine compounds (33, 34), the nutritional and chemical aspects of pteroylglutamic acid (35 to 40), and the various dietary factors concerned in erythropoiesis (41).

The effectiveness of pteroylglutamic acid in eliciting a hematologic remission in pernicious anemia has now been amply demonstrated (35 to 41). It is generally agreed that the initial hematologic response is indistinguishable from that which follows the administration of refined liver extract (36, 37, 42, 43), although a few patients have been reported in whom the response was suboptimal (44, 45). Observations on patients treated with pteroylglutamic acid for a period of one to two years indicate that good hematologic remissions are not maintained in every instance nor is glossitis always prevented (46, 47, 48). Several reports have suggested that the administration of this vitamin in conjunction with liver extract may produce a better hematologic response than either substance alone (44, 49, 50). It has now been demonstrated repeatedly that the neurologic manifestations of pernicious anemia are, in many patients, neither prevented nor alleviated by the administration of pteroylglutamic acid (43 to 54). Ross *et al.* (49) have suggested that this substance may actually precipitate or aggravate the neurologic disease by interfering with the metabolism of glutamic acid. Direct evidence of this has not been presented. Franklin and his co-workers (55) have been unable to demonstrate an inhibitory effect of pteroylglutamic acid on the metabolism of brain tissue *in vitro*.

Studies continue to be reported regarding the efficacy of pteroylglutamic acid in relieving the hematologic abnormalities of tropical and nontropical sprue (37, 56). Darby and co-workers (57, 58) have observed not only hematologic remissions but also relief of glossitis, cessation of diarrhea, and improved gastrointestinal absorption. It is suggested that pteroylglutamic acid is essential in maintaining normal gastrointestinal absorption.

In contrast to the above reports Weir & Comfort (59) and Davidson *et al.* (60) have not observed significant improvement in the

intestinal manifestations and noted only moderate transient improvement in the hematologic manifestations of nontropical sprue. Thus it would seem that not all patients with sprue are benefited markedly by such therapy. Davidson *et al.* (60) suggest that the Cuban patients studied by Spies represent cases of primary nutritional macrocytic anemia with secondary steatorrhea, whereas the patients studied in Scotland represent cases of primary (genetic) jejuno-ileal insufficiency with nutritional deficiencies secondary to the bowel abnormalities.

Pteroylglutamic acid has now been demonstrated to be effective in the treatment of macrocytic anemia associated with gastrointestinal resections (50, 61), megaloblastic anemia of infancy (62, 63), "achrestic" anemia (40), megaloblastic anemia of pregnancy (64), nontropical nutritional macrocytic anemia (65), tropical macrocytic anemia (66, 67, 68), refractory megaloblastic anemia (69, 70, 71, 72), and macrocytic anemia caused by *Diphyllobothrium latum* (73).

It may now be possible to divide the various macrocytic, megaloblastic anemias which have been reported from various parts of the world into two types on the basis of their response to purified liver extract and pteroylglutamic acid. Group one, representing those anemias which respond to either the antipernicious anemia factor or pteroylglutamic acid, includes Addisonian pernicious anemia, sprue, nontropical nutritional macrocytic anemia, macrocytic anemia associated with gastrointestinal resections, megaloblastic anemia of infancy, and macrocytic anemia caused by *D. latum*. Group two includes those anemias which respond only to pteroylglutamic acid and consists of "achrestic" anemia, megaloblastic anemia of pregnancy, tropical macrocytic anemia, and "refractory megaloblastic" anemia.

In addition to these two antianemic substances in liver, it has been suggested that proteolyzed liver contains a third (69). However, the identity of this substance as distinct from pteroylglutamic acid has not as yet been demonstrated conclusively (69).

The relation between pteroylglutamic acid and the antipernicious anemia factor of liver is still obscure. Several theories have been proposed but none explain all the facts (36). Whether or not patients with pernicious anemia respond to pteroylheptaglutamic acid is not clear (35, 36, 37, 74), but it is known that neither pteroylglutamic acid nor its three known polyglutamates are the

extrinsic factor, the intrinsic factor, or the antipernicious anemia factor of liver. A close relation between pteroylglutamic acid and nucleic acid metabolism has been suggested by studies in bacterial systems (75 to 81) and by the fact that patients with pernicious anemia respond to large doses of thymine (82). Spies *et al.* have administered adenine (83), methylpteroylglutamic acid, formylpteroic acid, pteroylaspartic acid, oxyfolic acid, and oxypteroic acid to patients with pernicious anemia and have found them to be inactive (84). Formylpteroylglutamic acid possessed some activity but was not as effective per unit of weight as was pteroylglutamic acid.

It is difficult to interpret and relate the various reported experiments in animals which have some connection with the antipernicious anemia type of liver extract and with pteroylglutamic acid. Nutritional macrocytic anemia has been produced experimentally in swine by Welch, Heinle and co-workers (85, 86), and by Cartwright *et al.* (87). The animals were fed highly purified diets deficient in pteroylglutamic acid and supplemented with a folic acid antagonist. The anemia was associated with a megaloblastic bone marrow, leukopenia, neutropenia, and a slight thrombocytopenia. The hematologic manifestations were rapidly alleviated by pteroylglutamic acid and, according to Heinle *et al.*, by purified liver extract. Cartwright *et al.* have not consistently observed a satisfactory response to purified liver extract. The Cleveland group (88) has demonstrated that the liver of a deficient pig was devoid of antipernicious anemia activity and that the administration of pteroylglutamic acid did not result in the synthesis of the antipernicious anemia factor.

Ruegamer *et al.* (89) following repeated nicotinic acid depletion in dogs receiving pteroylglutamic acid have produced an anemia which responds to small amounts of purified liver extract. Rats given a diet deficient in protein have been observed by Daft (90) to develop anemia, leukopenia, and granulocytopenia which respond to either pteroylglutamic acid or "15 unit" liver extract. This has been confirmed by others (91, 92, 93). Antipernicious anemia liver extract has been found to be active in promoting the growth of chicks (94). It has been reported that xanthopterin (95), pteroylglutamic acid (96), and pteroylheptaglutamic acid (97) are effective in relieving the blood dyscrasias induced by sulfonamides in rats.

It was reported by Davis & Hamilton (98) that the administration of pteroylglutamic acid to normal human subjects results in an increase in serum cholinesterase activity. This has not been confirmed by Kunkel *et al.* (99) or by Hawkins (100). Furthermore, Kunkel and his group were unable to confirm the studies in which Davis reported that the administration of acetylcholine to dogs resulted in the development of macrocytic anemia which responded to liver extract therapy (101). The erythrocytes of patients with pernicious anemia in relapse are abnormally low in cholinesterase activity and the plasma exhibits a subnormal esterase activity (102, 103, 104). The administration of liver extract or pteroylglutamic acid is immediately followed by an increase in the cholinesterase activity of the red cells. However, there is little to support the hypothesis (105, 106) that the acetylcholine-cholinesterase system is fundamentally concerned in the pathogenesis of macrocytic anemias. In fact, Grob *et al.* (104) have observed complete remissions in pernicious anemia following specific therapy in spite of the sustained suppression of plasma and red cell esterase activity by the daily administration of di-isopropyl fluorophosphate.

An alteration in tyrosine metabolism in pernicious anemia is indicated by the studies of Swendseid *et al.* (107). Patients in relapse were found to excrete large quantites of urinary phenol. Within forty-eight hours after therapy the excretion of hydroxyphenyl acid was reduced to the normal values. A relationship between purified liver extract and pteroylglutamic acid and tyrosine metabolism is also suggested by studies in animals (108, 109, 110).

An elevation in plasma catalase has been found in patients with pernicious anemia (111). A prompt fall to normal values occurred coincidentally with the reticulocyte response.

Further studies on the intrinsic factor have been published (112 to 115). Ågren & Waldenström (115) have identified the intrinsic factor as an aminopolypeptidase. The incubation of beef muscle in purified aminopolypeptidase solutions was found to result in the production of a factor capable of inducing remissions in patients with pernicious anemia.

A number of compounds, chemically similar to pteroylglutamic acid, which function as metabolic antagonists, have been synthesized (116 to 124). These substances are now being used clinically as well as experimentally.

Reticulocyte-ripening substances.—A series of researches begun in Copenhagen in 1941 by Plum and his co-workers (125 to 134) have yielded interesting data regarding factors concerned in the ripening of reticulocytes. Plum found that reticulocytes suspended in saline disappeared slowly but that the rate of disappearance could be accelerated considerably by adding commercial liver extract to the saline in which the cells were suspended. This ripening process followed the equation for the rate of a monomolecular reaction and experiments with varying concentrations of liver extract showed that the constant was proportional to the concentration of the liver extract. Jacobsen & Plum (127) found that the reticulocyte-ripening principle from liver consisted of two fractions, a thermostable factor and a thermolabile factor, each inactive without the other. The thermostable factor has been identified as L-tyrosine. Further investigations on the metabolism of the thermostable factor have shown that dioxyphenylalanine and hallochrom, both oxygenated products of tyrosine, have a much stronger activating effect than tyrosine. Hallochrom was found to be fifty to one hundred times more active than tyrosine. Since enzymes are present in red cells which are capable of converting tyrosine to hallochrom, these investigators postulate that the activity of tyrosine is due to its conversion to hallochrom. The thermolabile factor has not been identified but a potent preparation from gastric tissue containing 70 to 80 per cent xanthine has been isolated. Synthetic xanthine when added to tyrosine was found to be partially active. Likewise, leukopterin and pteroylglutamic acid were found to be active, especially in combination with tyrosine. Since the last two compounds are heat stable, it is unlikely that they represent the thermolabile factor. Jacobsen (126) states that the effect of gastric extract cannot be accounted for by its content of xanthine but that possibly a tautomeric isomer of xanthine is the thermolabile factor. Large amounts of this factor have been found in extracts of stomach, duodenum, and jejunum, apparently in relation to the distribution of Brunner's glands (128). Further studies have suggested that the thermolabile factor is formed principally in the stomach and is then transported to the reticulo-endothelial system where it is transformed by the action of tyrosine, or an oxygenated derivative of tyrosine, into the mature active ripening substance which is found in plasma. It has been further postulated by Christensen & Plum (129), and a certain amount of circumstantial

evidence has been presented, that the pituitary-thyroid axis is concerned with the activation of the ripening substances. The relative amounts of the reticulocyte-ripening factor in the plasma of different animals and in various physiologic and pathologic states in man have been measured (130 to 134). In general, a decrease has been found in untreated pernicious anemia, hyperthyroidism, hypothyroidism, and in cachectic states. An increase has been found in infancy, during rapid blood regeneration following hemorrhage, in iron deficiency states and during menstruation.

The implications of these studies are important. If the observations are substantiated, it is obvious that the reticulocyte percentage in the peripheral blood depends not only upon the output of reticulocytes from the bone marrow but also upon the rate of ripening in the blood stream. Thus if the reticulocyte-ripening principle were diminished a slight reticulocytosis would not necessarily indicate an increase in blood production. Such a theory might also explain why certain types of anemia are associated with a more profound reticulocytosis during response to therapy than are others; for example, compare pernicious anemia and iron deficiency anemia.

Hormones and other factors.—Hays (135, 136) has studied a factor contained in highly purified liver extracts which, when added to *in vitro* cultures of rat bone marrow, produces an increase in reticulocytes. This factor appears to be concerned with the maturation of normoblasts into reticulocytes and is consequently distinct, on the basis of its physiologic properties, from the factors studied by Plum.

Present knowledge concerning the relation of the endocrine system to hematopoiesis has been summarized by Gordon & Charipper (137). They conclude that certain of the endocrine glands undoubtedly exert an influence on the process of blood formation but that in general the effects are complex and controversial and more carefully controlled experiments are needed. They suggest the interesting hypothesis that anoxia may result in the release of hormones which stimulate the bone marrow.

Crafts (138) has observed marked changes in the bone marrow of dogs following the administration of large doses of estrogens. Initially there was a great increase in the neutrophilic elements which was followed by their discharge into the peripheral blood, resulting in a leukocytosis. This stage was followed by destruction

of the leukocytic elements in the marrow and finally by complete destruction of all the myeloid and erythroid tissue and replacement by "edema."

The feeding of deaminized casein to rats results in a profound anemia, as pointed out by Hogan & Ritchie [(139) see also (41)] as early a 1934. It was soon discovered that the anemia could be either prevented or alleviated by the inclusion of lysine in the diet. However, since it was necessary to administer two to four times the normal requirement of lysine, Hogan *et al.* speculated that the the anemia was not due to a deficiency but rather to the presence of a toxic substance in the casein which was detoxified by lysine. The toxic substance has now been isolated and identified as α-amino-ε-hydroxycaproic acid, an intermediate compound in the *in vitro* synthesis of lysine (140).

Studies have appeared on the effects of nicotinic acid (141), pantothenic acid (142), choline (143, 144), pyridoxine (145), ascorbic acid (146), amino acids (147, 148, 149), protein (150, 151), castration (152), hypophysectomy (153), and unidentified factors (154) on erythropoiesis.

Iron metabolism.—Granick (5) and Michaelis (155) have summarized their concept of the mechanism for the control of iron absorption by the mucosal cells. According to this theory, there exists in the mucosal cell an equilibrium between the ferrous iron of the cell and the ferric iron of ferritin. As the concentration of iron in the serum falls, ferrous iron leaves the mucosal cell, resulting in a diminution of ferritin in the mucosa. When the ferritin has decreased to a point where the cell is no longer "physiologically saturated" with respect to ferrous iron, more iron is absorbed into the cells. According to this theory, the intestinal mucosa is one of the major regulators of iron metabolism by virtue of its ability to accept or reject iron according to the needs of the organism. The theory explains satisfactorily the observation that iron-deficient subjects absorb more iron than do normal persons, but, as pointed out by Dubach *et al.* (156), it does not explain adequately the fact demonstrated by them that patients with pernicious anemia in relapse, with refractory anemia, or with hemolytic anemia, absorb moderately large amounts of iron even though their tissue stores are adequate. These workers conclude that although the mucosal block theory remains the best explanation for all the known facts it does not apply to all pathological states.

Knowledge concerning the transportation of iron has recently been extended by the discovery that this metal is bound in the plasma by a specific protein. This protein, referred to by Cohn (157) as the metal-combining protein, has been purified, characterized, and crystallized and found to be a β_1-globulin (Fraction IV-7) with a molecular weight of about 90,000. One molecule is capable of binding two molecules of either ferrous or ferric iron. The iron content of the protein is about 0.125 per cent. Studies over a wide range of pH have revealed that the iron is firmly bound at neutral pH but dialyzable at acid pH. Laurell (158) has published a comprehensive monograph on the iron-binding component in human plasma. In one hundred normal subjects the mean value for the iron binding capacity of the serum was 315 ± 3.3 μg. per cent. In pregnancy, infectious hepatitis, and acute and chronic blood loss the capacity of the serum to bind iron was found to be increased. In acute and chronic infections, pernicious anemia, hemolytic anemia, cirrhosis of the liver, uremia, and malignancy this capacity was found to be diminished. On the basis of these results, Laurell has advanced the hypothesis that the body is capable of mobilizing iron from the depots and, at the same time, can increase the absorption of iron by either lowering the serum iron concentration or by increasing the iron-binding component of the serum; conversely, by either increasing the serum iron or lowering the iron-binding protein component, more iron can be transferred to the depots and the absorption of iron checked.

Vaughan (159) has reviewed present knowledge of the pathogenesis of the anemia associated with sepsis. Studies on this subject have continued in Wintrobe's laboratory (25). It has been reported that by the simultaneous administration of cobalt to rats the anemia associated with inflammation could be prevented from developing and polycythemia appeared instead (160). The adrenal gland has no effect on the normal level of plasma iron in rats, nor does it affect the hypoferremia which is observed in animals following turpentine injections (161).

Bone Marrow

Technique.—General (162 to 166); spinous process (167); relative fat content (168); cellularity (169); culture (170).

Pizzolato & Stasney (171) in thirty patients with a wide variety of pathologic conditions aspirated two samples of human sternal

marrow simultaneously and compared the two samples as to the percentage of the different cells, the total number of nucleated cells, and the myeloid-erythroid ratio. There were wide variations in the two specimens but the trend as determined by the myeloid-erythroid ratio was always similar. The authors concluded that morphologic or pathologic appraisal of any one region of the marrow will usually reveal trends in other portions of the marrow.

Myelograms.—Normal myelograms have been defined for rats (172), mice (173), and humans (164, 174). Myelograms have been described in polycythemia (175), congenital hemolytic icterus in crisis (176), arthritis (177), renal disease (178), brucellosis (179), pernicious anemia (180), and macrocytic anemia of infancy (181).

Physiology.—The concept that the bone marrow is, under normal circumstances, largely regulated by the oxygen tension in this organ has now been challenged by several observers. Rosin & Rachmilewitz (182) determined the effect of various oxygen tensions on explanted bone marrow fragments and found that, under conditions of low oxygen tension, degeneration took place whereas, under conditions of increased oxygen tension, an increased rate of maturation and multiplication occurred. Grant & Root (183, 184), by directly observing the oxygen saturation of blood in red bone marrow during a period of constant and severe erythropoietic stimulation, found that vigorous erythropoiesis was not necessarily associated with a lowered oxygen saturation of the blood circulating through the marrow.

The metabolism of bone marrow has been studied by Goldinger, Lipton & Barron (185), who report that, although marrow is the site of great cellular activity, the Q_{O_2} values resemble those of tissues with low respiration. Of the numerous substrates added, only glucose, pyruvate, and acetate were utilized vigorously. These authors present evidence that carbohydrate utilization in the marrow in the presence of oxygen is directed towards the oxidation of pyruvate to acetate. They found the respiration of bone marrow to be increased on addition of boiled yeast juice but not pteroylglutamic acid. Bird & Evans (186) have studied the effect of pH on the aerobic acid production of rabbit bone marrow and have found considerable depression with increasing acidity.

Using microspectrographic techniques Thorell (187) has analyzed quantitatively the cytochemical processes involved in the formation of cellular substances in living bone marrow cells. His

excellent monograph deserves careful reading and study by those interested in this subject. In brief, Thorell found that the new formation of cellular proteins during hematopoiesis takes place at an early stage of development in the presence of high concentrations of ribose polynucleotides in the cytoplasm and nucleolar apparatus. During blood cell maturation the ribose polynucleotide-containing nucleolar mass and the concentration of cytoplasmic polynucleotides decreases continuously, parallel with a declining growth activity of the cell. This declining growth activity during maturation is postulated as being regulated by a definite part of the chromatin which, during the interphase, can be defined as the nucleolus-associated chromatin. The endocellular synthesis of hemoglobin starts after the ribose polynucleotide metabolism is completed and thereafter increases rapidly. In leukemia he found a measurable increase in ribose polynucleotide metabolism in association with the new formation of cellular proteins. In iron deficiency the decrease in the polynucleotide metabolism of the cell proceeded normally but hemoglobin synthesis was greatly retarded. In pernicious anemia the ribose polynucleotides of the cytoplasm and the nucleolar apparatus failed to disappear. The formation of hemoglobin seemed to take place normally in this condition.

Plum (170) has offered the concept that the formation of erythrocytes takes place not solely by mitotic division but also by disunion of cytoplasmic pseudopodia from normoblasts. He offers, as evidence of this, the fact that the mitotic cells counted in bone marrow cultures account for only about 1 per cent of the erythrocytes. When the mitotic activity was arrested by colchicine the production of red cells continued. By direct observation in a small culture chamber under the microscope he was able to see a spherical normoblast become oval, with the nucleus at one end and the protoplasm flowing toward the opposite end where, suddenly, a portion of it detached, becoming a small erythrocyte.

With the aid of *in vitro* cultures of bone marrow, Plum (170, 188, 189) found that normal plasma as well as liver extracts contain substances which stimulate erythropoiesis. Plasma from subjects anemic as a result of hemorrhage contained substances which markedly stimulated erythropoiesis. The greater the anemia, the greater the stimulation. Marrow from a patient with pernicious anemia showed increased erythropoiesis *in vitro* when nourished by normal serum, whereas serum from the patient lowered the

erythropoiesis of normal marrow. The addition of liver extract to the serum of the patient with pernicious anemia made possible normal erythropoiesis. Norris & Majnarich (190) have found that xanthopterin causes an increase in the rate of cellular proliferation when added to bone marrow suspensions.

Hypersplenism.—The relation between splenic activity and bone marrow function continues to be one of the most challenging problems in hematology. By no means understood, this problem has engaged the interest of clinicians, biochemists, and physiologists. Dameshek & Estren (191), in a monograph on the subject, restate their views that the spleen produces hormones which inhibit the formation and emission of cells in and from the bone marrow. Doan and his co-workers (192) strongly maintain that the spleen is primarily concerned with the sequestration and phagocytosis of cells in the splenic parenchyma. Some evidence has been presented that the thrombocytopenia observed in kala-azar (193) and in idiopathic thrombocytopenic purpura (194) is the result of diminished production of platelets by the megakaryocytes in the marrow.

LITERATURE CITED

1. FISCHER, H., AND SIEDEL, W., *FIAT Review of German Science* (Biochemistry), Part I, 109–27 (1947)
2. FISCHER, H., AND V. DOBENECK, H., *FIAT Review of German Science* (Biochemistry), Part I, 129–39 (1947)
3. FISCHER, H., AND STRELL, M., *FIAT Review of German Science* (Biochemistry), Part I, 141–86 (1947)
4. GRANICK, S., AND GILDER, H., *Advances in Enzymol.*, **7**, 305–68 (1947)
5. GRANICK, S., *Ann. N. Y. Acad. Sci.*, **48**, 657–81 (1947)
6. WATSON, C. J., AND LARSON, E. A., *Physiol. Revs.*, **27**, 478–510 (1947)
7. SHACK, J., AND CLARK, W. M., *J. Biol. Chem.*, **171**, 143–87 (1947)
8. GRINSTEIN, M., AND WINTROBE, M. M., *J. Biol. Chem.*, **172**, 459–67 (1948)
9. GRINSTEIN, M., *J. Biol. Chem.*, **167**, 515–19 (1947)
10. SHEMIN, D., AND RITTENBERG, D., *J. Biol. Chem.*, **166**, 621–25 (1946)
11. ALTMAN, K. I., CASARETT, G. W., MASTERS, R. E., NOONAN, T. R., AND SOLOMAN, K., *Federation Proc.*, **7**, 2 (1948)
12. GRINSTEIN, M., KAMEN, M. D., AND MOORE, C. V., *J. Biol. Chem.*, **174**, 767–68 (1948)
13. SHEMIN, D., LONDON, I. M., AND RITTENBERG, D., *J. Biol. Chem.*, **173**, 799–800 (1948)
14. LONDON, I. M., SHEMIN, D., AND RITTENBERG, D., *J. Biol. Chem.*, **173**, 797–98 (1948)
15. FISCHER, H., AND FINK, E., *Z. physiol. Chem.*, **280**, 123–26 (1944)
16. BLOCK, K., AND RITTENBERG, D., *J. Biol. Chem.*, **159**, 45–58 (1945)
17. GRANICK, S., AND GILDER, H., *J. Gen. Physiol.*, **30**, 1–13 (1946)
18. GILDER, H., AND GRANICK, S., *J. Gen. Physiol.*, **31**, 103–17 (1947)
19. WATSON, C. J., *Blood*, **1**, 99–120 (1946)
20. TOTTER, J. R., SIMS, E., AND DAY, P. L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 7–9 (1947)
21. TOTTER, J. R., AND SIMS, E. S., *Federation Proc.*, **7**, 196 (1948)
22. STEINKAMP, R. C., SHUKERS, C. F., TOTTER, J. R., AND DAY, P. L., *Federation Proc.*, **6**, 295 (1947)
23. CARTWRIGHT, G. E., AND WINTROBE, M. M., *J. Biol. Chem.*, **172**, 557–65 (1948)
24. GRINSTEIN, M., SILVA, J. A., AND WINTROBE, M. M., *J. Clin. Invest.*, **27**, 245–59 (1948)
25. CARTWRIGHT, G. E., HUGULEY, C. M., ASHENBRUCKER, H., FAY, J., AND WINTROBE, M. M., *Blood*, **3**, 501–25 (1948)
26. FOLKERS, K., *Science*, **107**, 396–97 (1948)
27. SHORB, M. S., *Science*, **107**, 397–98 (1948)
28. SHORB, M. S., *J. Biol. Chem.*, **169**, 455–56 (1947)
29. WEST, R., *Science*, **107**, 398 (1948)
30. SPIES, T. D., STONE, R. E., AND ARAMBURU, T., *Southern Med. J.*, **41**, 522–23 (1948)
31. SPIES, T. D., LOPEZ, G. G., MILANES, F., TOCA, R. L., AND CULVER, B., *Southern Med. J.*, **41**, 523–25 (1948)
32. SMITH, E. L., *Nature*, **161**, 638–39 (1948)

33. GATES, M., *Chem. Revs.*, **41**, 63–95 (1947)
34. BIELIG, H. J., *FIAT Review of German Science* (Biochemistry), Part I, 67–108 (1947)
35. JUKES, T. H., AND STOKSTAD, E. L. R., *Physiol. Revs.*, **28**, 51–106 (1948)
36. WELCH, A. D., *Federation Proc.*, **6**, 471–79 (1947)
37. DARBY, W. J., *Vitamins & Hormones*, **5**, 119–61 (1947)
38. SARGENT, F., *New Engl. J. Med.*, **237**, 667–72, 703–7 (1947)
39. DAMESHEK, W., *New Engl. J. Med.*, **237**, 434–41, 480–84 (1947)
40. WILKINSON, J. F., *Brit. Med. J.*, **I**, 771–76, 822–27 (1948)
41. CARTWRIGHT, G. E., *Blood*, **2**, 111–53, 256–98 (1947)
42. FROMMEYER, W. B., AND SPIES, T. D., *Am. J. Med. Sci.*, **213**, 135–49 (1947)
43. HEINLE, R. W., DINGLE, J. T., AND WEISBERGER, A. S., *J. Lab. Clin. Med.*, **32**, 970–81 (1947)
44. MEYER, L. M., *Blood*, **2**, 50–62 (1947)
45. HALL, B. E., AND WATKINS, C. H., *J. Lab. Clin. Med.*, **32**, 622–34 (1947)
46. VILTER, R. W., VILTER, C. F., AND HAWKINS, V., *J. Lab. Clin. Med.*, **32**, 1426–27 (1948)
47. SCHWARTZ, S. O., AND ARMSTRONG, B. E., *J. Lab. Clin. Med.*, **32**, 1427 (1948)
48. HANSEN-PRUSS, O. C., *Am. J. Med. Sci.*, **214**, 465–68 (1947)
49. ROSS, J. F., BELDING, H., AND PAEGEL, B. L., *Blood*, **3**, 68–90 (1948)
50. DAMESHEK, W., *Blood*, **3**, 699–701 (1948)
51. WAGLEY, P. F., *New Engl. J. Med.*, **238**, 11–15 (1948)
52. BETHELL, F. H., AND STURGIS, C. C., *Blood*, **3**, 57–67 (1948)
53. VILTER, C. F., VILTER, R. W., AND SPIES, T. D., *J. Lab. Clin. Med.*, **32**, 262–73 (1947)
54. HEINLE, R. W., AND WELCH, A. D., *J. Am. Med. Assoc.*, **133**, 739–41 (1947)
55. FRANKLIN, A. L., REGAN, M., LEWIS, D., STOKSTAD, E. L. R., AND JUKES, T. H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 523–27 (1948)
56. SUÁREZ, R. M., SPIES, T. D., AND SUÁREZ, R. M., JR., *Ann. Internal Med.*, **26**, 643–77 (1947)
57. DARBY, W. J., JONES, E., WARDEN, H. F., AND KASER, M. M., *J. Nutrition*, **34**, 645–60 (1947)
58. DARBY, W. J., KASER, M. M., AND JONES, E., *J. Nutrition*, **33**, 243–50 (1947)
59. WEIR, J. F., AND COMFORT, M. W., *J. Lab. Clin. Med.*, **32**, 1231–41 (1947)
60. DAVIDSON, L. S. P., GIRDWOOD, R. H., AND INNES, E. M., *Lancet*, **I**, 511–15 (1947)
61. MORGANS, M. E., RIMINGTON, C., AND WHITTAKER, N., *Lancet*, **II**, 128 (1947)
62. ZUELZER, W. W., *J. Am. Med. Assoc.*, **134**, 998–1007 (1947)
63. SIEBENTHAL, B. J., *J. Pediat.*, **32**, 188–92 (1948)
64. DAVIDSON, L. S. P., GIRDWOOD, R. H., AND CLARK, J. R., *Brit. Med. J.*, **I**, 819–22 (1948)
65. SPIES, T. D., LOPEZ, G. G., MILANES, F., STONE, R. E., TOCA, R. L., AND ARAMBURU, T., *Lancet*, **I**, 239–41 (1948)
66. WILLS, L., *Blood*, **3**, 36–56 (1948)
67. GOODALL, J. W. D., GOODALL, H. I., AND BANERJEE, D., *Lancet*, **I**, 20–21 (1948)
68. KEMP, T. A., *Lancet*, **II**, 350–53 (1947)

69. DAVIDSON, L. S. P., *Blood*, **3**, 107–20 (1948)
70. DAVIDSON, L. S. P., AND GIRDWOOD, R. H., *Brit. Med. J.*, **I**, 587–91 (1947)
71. DAVIDSON, L. S. P., AND GIRDWOOD, R. H., *Lancet*, **I**, 360–63 (1948)
72. WALDENSTRÖM, J., *Blood*, **2**, 426–39 (1947)
73. VON BONSDORFF, B., *Blood*, **3**, 91–102 (1948)
74. SHARP, E. A., AND VONDER HEIDE, E. C., *Am. J. Clin. Path.*, **17**, 761–69 (1947)
75. ROGERS, L. L., AND SHIVE, W., *J. Biol. Chem.*, **172**, 751–58 (1948)
76. HITCHINGS, G. H., ELION, G. B., VANDER WERFF, H., AND FALCO, E. A., *J. Biol. Chem.*, **174**, 765–66 (1948)
77. LAMPEN, J. O., AND JONES, M. J., *J. Biol. Chem.*, **170**, 133–46 (1957)
78. STOKSTAD, E. L. R., REGAN, M., FRANKLIN, A. L., AND JUKES, T. H., *Federation Proc.*, **7**, 193 (1948)
79. HITCHINGS, G. H., ELION, G. B., AND VANDER WERFF, H., *Federation Proc.*, **7**, 160 (1948)
80. KALCKAR, H. M., AND KLENOW, H., *J. Biol. Chem.*, **172**, 349–52 (1948)
81. KALCKAR, H. M., KJELDGAARD, N. O., AND KLENOW, H., *J. Biol. Chem.*, **174**, 771–72 (1948)
82. FROMMEYER, W. B., AND SPIES, T. D., *Am. J. Med. Sci.*, **213**, 135–49 (1947)
83. STONE, R. E., AND SPIES, T. D., *Am. J. Med. Sci.*, **215**, 411–14 (1948)
84. SPIES, T. D., LOPEZ, G. G., STONE, R. E., MILANES, F., BRANDENBURG, R. O., AND ARAMBURU, T., *Blood*, **3**, 121–26 (1948)
85. WELCH, A. D., HEINLE, R. W., SHARPE, G., GEORGE, W. L., AND EPSTEIN, M., *Proc. Soc. Exptl. Biol. Med.*, **65**, 364–68 (1947)
86. HEINLE, R. W., WELCH, A. D., GEORGE, W. L., EPSTEIN, M., AND PRITCHARD, J. A., *J. Lab. Clin. Med.*, **32**, 1398 (1947)
87. CARTWRIGHT, G. E., FAY, J., TATTING, B., AND WINTROBE, M. M., *J. Lab. Clin. Med.*, **33**, 397–416 (1948)
88. WELCH, A. D., HEINLE, R. W., PRITCHARD, J. A., AND SALIS, H., *Federation Proc.*, **7**, 300 (1948)
89. RUEGAMER, W. R., TORBET, N., AND ELVEHJEM, C. A., *Federation Proc.*, **6**, 287 (1947)
90. DAFT, F. S., *U. S. Pub. Health Service, Pub. Health Repts.*, **62**, 1785–92 (1947)
91. EMERSON, G. A., AND MUSHETT, C. W., *Federation Proc.*, **7**, 285 (1948)
92. MUSHETT, C. W., AND EMERSON, G. A., *Federation Proc.*, **7**, 295 (1948)
93. SHEHATA, O., AND JOHNSON, B. C., *Proc. Soc. Exptl. Biol. Med.*, **67**, 332–35 (1948)
94. NICHOL, C. A., ROBBLEE, A. R., CRAVENS, W. W., AND ELVEHJEM, C. A., *J. Biol. Chem.*, **170**, 419–20 (1947)
95. NORRIS, E. R., AND MAJNARICH, J. J., *Am. J. Physiol.*, **152**, 179–82 (1948)
96. PETERING, H. G., DELOR, R. A., AND MURRAY, H. C., *Blood*, **2**, 440–50 (1947)
97. SWENDSEID, M. E., BROWN, R. A., BIRD, O. D., AND HEINRICH, R. A., *Arch. Biochem.*, **16**, 367–71 (1948)
98. DAVIS, J. E., AND HAMILTON, W. M., *Federation Proc.*, **6**, 95 (1947)
99. KUNKEL, A. M., KROP, S., AND WESCOE, W. C., *Am. J. Physiol.*, **152**, 309–13 (1948)
100. HAWKINS, R. D., *Arch. Biochem.*, **17**, 97–104 (1948)

101. DAVIS, J. E., *Am. J. Physiol.*, **147**, 404–11 (1946)
102. MEYER, L. M., SAWITSKY, A., RITZ, N. D., AND FITCH, H. M., *J. Lab. Clin. Med.*, **33**, 189–202 (1948)
103. CLINE, J. K., JOHNSON, R. B., AND JOHNSON, W. H., *Southern Med. J.*, **41**, 374–76 (1948)
104. GROB, D., LILIENTHAL, J. L., JR., HARVEY, A. M., AND JONES, B. F., *Bull. Johns Hopkins Hosp.*, **81**, 217–44 (1947)
105. DAVIS, J. E., *Am. J. Digestive Diseases*, **15**, 52–55 (1948)
106. BARNARD, R. D., AND MENTHA, J. W., *Science*, **107**, 195–96 (1948)
107. SWENDSEID, M. E., WANDRUFF, B., AND BETHELL, F. H., *J. Lab. Clin. Med.*, **32**, 1242–50 (1947)
108. RODNEY, G., SWENDSEID, M. E., AND SWANSON, A. L., *J. Biol. Chem.*, **168**, 395–96 (1947)
109. WOODRUFF, C. W., AND DARBY, W. J., *J. Biol. Chem.*, **172**, 851–52 (1948)
110. SEALOCK, R. R., AND LEPOW, J. P., *J. Biol. Chem.*, **174**, 763–64 (1948)
111. DILLE, R. S., AND WATKINS, C. H., *J. Lab. Clin. Med.*, **33**, 480–96 (1948)
112. LANDBOE-CHRISTENSEN, E., AND BOHN, C. L. S., *Acta Med. Scand.*, **127**, 116–29 (1947)
113. LANDBOE-CHRISTENSEN, E., AND PLUM, C. M., *Am. J. Med. Sci.*, **215**, 17–23 (1948)
114. BENJAMIN, B., *Am. J. Diseases Children*, **75**, 143–89 (1948)
115. ÅGREN, G., AND WALDENSTRÖM, J., *Acta Med. Scand.*, **128**, Suppl. 196, 432–55 (1947)
116. FRANKLIN, A. L., STOKSTAD, E. L. R., BELT, M., AND JUKES, T. H., *J. Biol. Chem.*, **169**, 427–35 (1947)
117. HUTCHINGS, B. L., MOWAT, J. H., OLESON, J. J., STOKSTAD, E. L. R., BOOTHE, J. H., WALLER, C. W., ANGIER, R. B., SEMB, J., AND SUBBAROW, Y., *J. Biol. Chem.*, **170**, 323–28 (1947)
118. DANIEL, L. J., NORRIS, L. C., SCOTT, M. L., AND HEUSER, G. F., *J. Biol. Chem.*, **169**, 689–97 (1947)
119. DANIEL, L. J., AND NORRIS, L. C., *J. Biol. Chem.*, **170**, 747–56 (1947)
120. DANIEL, L. J., SCOTT, M. L., NORRIS, L. C., AND HEUSER, G. F., *J. Biol. Chem.*, **173**, 123–35 (1948)
121. EDWARDS, P. C., STARLING, D., MATTOCKS, A. M., AND SKIPPER, H. E., *Science*, **107**, 119–120 (1948)
122. WOOLLEY, D. W., AND PRINGLE, A., *J. Biol. Chem.*, **174**, 327–33 (1948)
123. FRANKLIN, A. L., STOKSTAD, E. L. R., AND JUKES, T. H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 398–400 (1948)
124. MARTIN, G. J., TOLMAN, L., AND MOSS, J., *Science*, **106**, 168 (1947)
125. KROGH, A., *Sci. Monthly*, **64**, 301–5 (1947)
126. JACOBSEN, E., *J. Clin. Path.*, **1**, 19–24 (1947)
127. JACOBSEN, E., AND PLUM, C. M., *Acta Physiol. Scand.*, **4**, 272–78 (1942)
128. PLUM, C. M., *Acta Med. Scand.*, **117**, 437–47 (1944)
129. CHRISTENSEN, B. G., AND PLUM, C. M., *Endocrinology*, **41**, 347–55 (1947)
130. PLUM, C. M., *Acta Physiol. Scand.*, **5**, 165–74 (1943)
131. PLUM, C. M., *Acta Med. Scand.*, **122**, 151–63 (1942)
132. PLUM, C. M., *Acta Physiol. Scand.*, **5**, 175–82 (1943)
133. PLUM, C. M., *Acta Physiol. Scand.*, **5**, 380–84 (1943)

134. PLUM, C. M., *Acta Physiol. Scand.*, **8**, 365–68 (1944)
135. HAYS, E. E., *Proc. Soc. Exptl. Biol. Med.*, **63**, 558–60 (1946)
136. HAYS, E. E., AND PAULSEN, E. C., *Federation Proc.*, **6**, 269 (1947)
137. GORDON, A. S., AND CHARIPPER, H. A., *Ann. N. Y. Acad. Sci.*, **48**, 615–37 (1947)
138. CRAFTS, R. C., *Blood*, **3**, 276–85 (1948)
139. HOGAN, A. G., AND RITCHIE, W. S., *J. Biol. Chem.*, **107**, 179–89 (1934)
140. PAGÉ, E., GAUDRY, R., AND GINGRAS, R., *J. Biol. Chem.*, **171**, 831–32 (1947)
141. WOOLEY, J. G., *Proc. Soc. Exptl. Biol. Med.*, **65**, 315–17 (1947)
142. ASHBURN, L. L., DAFT, F. S., AND FAULKNER, R. R., *Blood*, **3**, 451–62 (1947)
143. ENGEL, R. W., *Federation Proc.*, **7**, 285 (1948)
144. DAVIS, L. J., AND BROWN, A., *Blood*, **2**, 407–25 (1947)
145. ARANOW, H., AND GOLDSMITH, E. D., *Yale J. Biol. Med.*, **19**, 995–98 (1947)
146. LEPP, A., MOORE, P. R., ELVEHJEM, C. A., AND HART, E. B., *Poultry Sci.*, **26**, 594–97 (1947)
147. YESHODA, K. M., AND DAMODARAN, M., *Biochem. J.*, **41**, 382–88 (1947)
148. PORTER, R. R., AND SANGER, F., *Biochem. J.*, **42**, 287–94 (1948)
149. MELAMPY, R. M., *Proc. Soc. Exptl. Biol. Med.*, **65**, 213–15 (1947)
150. METCOFF, J., DARLING, D. B., SCANLON, M. H., AND STARE, F. J., *J. Lab. Clin. Med.*, **33**, 47–66 (1948)
151. LEHMANN, H., *Brit. J. Exptl. Path.*, **28**, 377 (1947)
152. CRUZ, W. O., AND UBATUBA, F., *Proc. Soc. Exptl. Biol. Med.*, **65**, 321–24 (1947)
153. CRAFTS, R. C., AND WALKER, B. S., *Endocrinology*, **41**, 340–46 (1947)
154. SHAEFER, A. E., TOVE, S. B., WHITEHAIR, C. K., AND ELVEHJEM, C. A., *J. Nutrition*, **35**, 147–66 (1948)
155. MICHAELIS, L., *Advances in Protein Chemistry*, **3**, 53–66 (1947)
156. DUBACH, R., CALLENDER, S. T. E., AND MOORE, C. V., *Blood*, **3**, 526–40 (1948)
157. COHN, E. J., *Blood*, **3**, 471–85 (1948)
158. LAURELL, C. B., *Acta Physiol. Scand.*, **14**, Suppl. 46, 1–129 (1947)
159. VAUGHAN, J., *Brit. Med. J.*, **I**, 35–48 (1948)
160. WINTROBE, M. M., GRINSTEIN, M., DUBASH, J. J., HUMPHREYS, S. R., ASHENBRUCKER, H., AND WORTH, W., *Blood*, **2**, 323–31 (1947)
161. MAJUMDER, D. N., AND WINTROBE, M. M., *J. Lab. Clin. Med.*, **33**, 532–41 (1948)
162. BERMAN, L., *Am. J. Clin. Path.*, **17**, 631–36 (1947)
163. BERMAN, L., AND AXELROD, A. R., *Am. J. Clin. Path.*, **17**, 61–66 (1947)
164. LUCIA, S. P., AND HUNT, M. L., *Am. J. Med. Sci.*, **213**, 686–93 (1947)
165. LIMARZI, L. R., *Am. Practitioner*, **2**, 514–22 (1948)
166. LIMARZI, L. R., *J. Lab. Clin. Med.*, **32**, 732–40 (1947)
167. LOGE, J. P., *Blood*, **3**, 198–204 (1948)
168. BERMAN, L., AND AXELROD, A. R., *Am. J. Clin. Path.*, **17**, 551–56 (1947)
169. BERMAN, L., AND AXELROD, A. R., *Am. J. Clin. Path.*, **17**, 557–60 (1947)
170. PLUM, C. M., *Blood*, **1**, 33–53 (1947)
171. PIZZOLATO, P., AND STASNEY, J., *J. Lab. Clin. Med.*, **32**, 741–48 (1947)
172. CAMERON, D. G., AND WATSON, G. M., *Blood*, **3**, 292–94 (1948)
173. ENDICOTT, K. M., AND GUMP, H., *Blood*, **1**, 60–63 (1947)

174. VAUGHAN, S. L., AND BROCKMYRE, F., *Blood*, **1**, 54–59 (1947)
175. MANNING, I. H., *Am. J. Med. Sci.*, **214**, 469–75 (1947)
176. OWREN, P. A., *Blood*, **3**, 231–48 (1948)
177. TRAUT, E. F., AND SCHWARTZ, S. O., *J. Lab. Clin. Med.*, **32**, 1430 (1947)
178. CALLEN, I. R., LIMARZI, L. R., AND LUETH, H. C., *J. Lab. Clin. Med.*, **32**, 1429–30 (1947)
179. SUNDBERG, R. D., AND SPINK, W. W., *Blood*, **1**, 7–32 (1947)
180. MALLARMÉ, J., *Blood*, **3**, 103–6 (1948)
181. ZUELZER, W. W., NEWHALL, A., AND HUTAFF, L., *J. Lab. Clin. Med.*, **32**, 1217–30 (1947)
182. ROSIN, A., AND RACHMILEWITZ, M., *Blood*, **3**, 165–74 (1948)
183. GRANT, W. C., AND ROOT, W.S., *Am. J. Physiol.*, **150**, 618–27 (1947)
184. GRANT, W. C., *Federation Proc.*, **7**, 43 (1948)
185. GOLDINGER, J. M., LIPTON, M. A., AND BARRON, E. S. G., *J. Biol. Chem.*, **171**, 801–11 (1947)
186. BIRD, R. M., AND EVANS, J. D., *Federation Proc.*, **7**, 145–46 (1948)
187. THORELL, B., *Acta Med. Scand.*, **129**, Suppl. 200, 1–120 (1947)
188. CLEMMESEN, J., ESPERSEN, T., AND PLUM, C. M., *Blood*, **3**, 155–64 (1948)
189. PLUM, C. M., *Acta Physiol. Scand.*, **14**, 383–98 (1947)
190. NORRIS, E. R., AND MAJNARICH, J. J., *Am. J. Physiol.*, **152**, 176–78 (1948)
191. DAMESHEK, W., AND ESTREN, S., *The Spleen and Hypersplenism*, 56 pp. (Grune and Stratton, New York, 1947)
192. DOAN, C. A., AND WRIGHT, C. S., *J. Lab. Clin. Med.*, **32**, 1399–1400 (1947)
193. CARTWRIGHT, G. E., CHUNG, H. L., AND CHANG, A., *Blood*, **3**, 249–75 (1948)
194. VALENTINE, E. H., *Am. J. Med. Sci.*, **214**, 260–67 (1947)

THE LYMPHATIC SYSTEM

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The literature reviewed in this chapter was selected chiefly from publications appearing since this subject was last presented in *The Annual Review of Physiology*, by Cope & Rosenfeld (1). This literature has proved to be extensive, largely as a result of a renewal and broadening of interest in the chemistry and physiology of normal and malignant lymphoid tissue. Notwithstanding the adoption of the suggestion of the editors that groups of selected papers rather than detailed literature be reviewed, it has nevertheless been necessary to compile a rather lengthy bibliography. The numerous clinical studies concerned with the treatment of lymphoid dyscrasias have been referred to only in a few instances in which the results seemed related to the topics under discussion.

Lymph—Circulation and Composition

Drinker & Hardenbergh (2) described certain of the anatomical features which influence absorption through the lung lymphatics. Experiments of four-hour duration in anesthetized dogs, in which the right lymphatic duct and thoracic duct had been cannulated and collection of lung lymph and blood specimens accomplished after intratracheal instillation of protein solutions, indicated that the absorption of such molecules was slight. Foreign particles (pyrex glass spheres averaging four micra in diameter) failed to pass into the lymph after such instillation. The authors concluded that the chief barrier to absorption is apparently the alveolar epithelium, since, when proteins were injected directly into lung tissue, and thus diffused widely in the alveolar walls, there was prompt delivery of these substances by the right lymphatic duct. The data are in agreement with those of Cameron & Courtice (3) and Courtice & Phipps (4). Gillman & Ivy (5) confirmed the important role which mesenteric lymphatics play in iron absorption and transport from the intestinal tract. These lymph channels were shown by Perry (6) to participate also in the transport of pancreatic lipase in pancreatic injury or disease. Haynes & Hardenbergh (7) found that continuous, intravenous injection of renin in

dogs over periods of one to three hours was without effect on cervical lymph flow.

Salter (8) reported that in cervical lymph the protein-bound iodine per gram of protein was concentrated relative to the homologous serum value. Brauer & Hardenbergh (9) examined the cholinesterase activity of lymph, lymph nodes, and lymphocytes. Liver injury in dogs increased the alkaline phosphatase and bilirubin content of both blood and lymph, according to Gonzalez-Oddone (10); no significant changes occurred in bile acids, total cholesterol, or cholesterol esters of either fluid. Landis (11) reviewed the problem of capillary permeability and the factors influencing the composition of capillary filtrate. McMaster (12) has provided an excellent description of the techniques and experiments performed in his laboratory in relation to the problems of interstitial fluid movement, lymph formation, and lymph flow. Drinker (13) discussed the role of the lymphatic circulation in the collection and distribution of extravascular protein.

Chemistry and Physiology of the Thymus

Although the thymus contains histological elements of a nonlymphoid nature, investigators continue to study thymus tissue as an approach to understanding the structure and function of lymphocytes and lymphoid organs. This is probably due to the availability of thymus tissue in large quantities for experiments designed to characterize the constituents of lymphocytes and lymphoid structures. Additional interest in the composition of the thymus stems from its classical use as source material for studies of nucleoproteins.

Proteins of the thymus.—Several laboratories have reported studies of proteins extractable from thymus tissue, with particular reference to the nucleoproteins and their degradation products. Mirsky & Pollister (14) extracted from the separated, washed nuclei of the cells of calf thymus tissue with 1 *M* NaCl, a desoxyribose nucleoprotein complex assigned the name chromosin. The product contained three components: desoxyribose nucleic acid, histone, and nonhistone protein. Chromosin is not a definite compound but a complex extracted from chromatin. Mirsky & Ris (15, 16) described a procedure for preparing masses of isolated chromosomes from calf thymus lymphocytes. After extraction with

alcohol and ether, the chromosomes contained 3.7 per cent phosphorus and 15.6 per cent nitrogen. Fractionation with 1 *M* NaCl gave two nucleoprotein-containing fractions; the soluble preparation consisted largely of desoxyribose nucleohistone and represented at least 90 per cent of the mass of the chromosomes. The insoluble residue contained approximately 12 per cent ribose, and 2 per cent desoxyribose nucleic acids. Stern (17) prepared the chromosomal desoxyribonucleoprotein of calf thymus by extraction with solvents of low ionic strength and purification by reprecipitation at 0.14 *M* NaCl concentration. Sodium arsenate and low temperatures inhibited the activity of thymonucleodepolymerase. The isolated product was homogenous in the Tiselius apparatus and in the ultracentrifuge; an approximate molecular weight of one million was estimated from sedimentation rate. The cytoplasm of calf thymus cells was reported to contain several globulin-like proteins, as well as appreciable amounts of ribonucleoprotein. Euler and his coworkers (18, 19, 20) have continued their studies of nucleoproteins by analysis of nucleoprotein preparations from calf thymus. Approximately 60 per cent of desoxyribonucleic acid was present. Tryptophane and tyrosine contents of three nucleoprotein samples were calculated from ultraviolet absorption spectroscopy data; values obtained were 0.28, 0.28, and 1.45 per cent for tyrosine, 0.25, 0.24, and 0.10 per cent for tryptophane. Molecular weights of 69,000 to 79,000 were reported for the nucleoprotein of thymus cell nuclei.

Extracts of human lymphoid tissue [Abrams & Cohen (21)] and of calf thymus, rabbit and rat lymphoid tissue, and mouse lymphosarcoma [Roberts & White (22)] have been examined electrophoretically. From six to eight protein components were seen; two of these accounted for the major portion of the total protein of the extracts. Application of cold alcohol fractionation at low temperatures to calf thymus tissue extracts (22) gave five fractions, four insoluble at alcohol concentrations of 10, 20, 30 and 40 per cent, respectively. The remaining supernatant solution, after dialysis and lyophilization, represented the fifth fraction. Electrophoretic examination of these fractions, and analyses for total nitrogen and phosphorus content, suggested that some degree of separation of the protein components of the crude extracts had been achieved. The histological distribution of the dipeptidases of the

thymus of young rats was examined by Praetorius (23), who concluded that the enzymes probably originate from reticulum cells.

Physiological effects of thymus constituents.—Kjerulf-Jensen (24) produced moderate thyroid hyperplasia in rats fed a stock diet supplemented with dried calf thymus. The goitrogenic material was insoluble in water and ethyl alcohol. Control feeding experiments with dried ox liver, dried beef, or dried cod spawn did not produce this effect. Roberts & White (22), on the basis of the working hypothesis that the lymphocyte, an end-cell of pituitary-adrenal cortical activity, might contain constituents which exert a suppressing action on the secretion of pituitary adrenotrophic hormone, found that daily intraperitoneal injections of crude thymus extracts for ten days produced evidence of lymphoid tissue hypertrophy in young rats. Ahlstrom & Euler (25) observed a marked toxic effect when the histones of thymus were injected intraperitoneally into young rats. Bloom and co-workers (26) prepared from thymus, by mild acid hydrolysis at elevated temperature, a basic protein containing 30 per cent of lysine and anthracidal *in vitro*. Weissman & Graf (27) demonstrated that calf thymus histone stopped the oxygen uptake of suspensions of anthrax bacilli. This anthracidal action of the histone was neutralized by thymus desoxyribonucleic acid.

Physiological roles of the thymus.—In addition to the above-mentioned studies of the effects of thymus extracts, other approaches have been made to the problem of the physiological role and function of the thymus. Andreasen & Ottesen (28), with the aid of radioactive phosphorus, showed that 5 to 6 per cent of thymus nucleic acid was turned over in three hours; lymph nodes and spleen showed only a 1 to 2 per cent turnover of nucleic acid during the same period. It was suggested that the thymus is the most important lymphocytopoietic organ. It is interesting in this connection that the sex difference in the total amount of lymphoid tissue in young, mature guinea pigs was found by Andreasen (29) to be most pronounced for thymus.

Efforts to establish a physiological role for the thymus by extirpation of the gland have been strikingly successful only in studies of experimental leukemia. Furth (30) has reviewed recently his classical work, demonstrating that thymectomy reduces markedly the incidence of spontaneous and induced leukemias in mice.

This problem has also been studied recently by Kaplan (31). Furth has suggested that the thymus may serve as the source of potentially malignant cells.

Thymectomy was reported by Cosma (32) to increase the urinary creatine of guinea pigs; death in sixty days followed thymus removal in experimentally cryptorchid guinea pigs. On the other hand, thymectomy failed to influence to any significant degree any of the following: neuromuscular atrophy and regeneration (33), nucleic acid content of liver (34), sensitivity of rats to deficiencies of vitamin A, vitamin D, or protein (35), the carbohydrate metabolism of normal (36) or diabetic rats (37), or the action of anterior pituitary extracts on the growth of rats (38). Andreasen (39) has reviewed and criticized the experiments of Bomskov, which suggested that the thymus exerted an endocrine influence on growth and carbohydrate metabolism.

Lymphoid Tissue Composition and Metabolism

Information concerning the constitutents of lymphocytes should aid in understanding the physiological significance of these cells. Studies of the composition of thymus tissue, particularly with respect to protein constituents, have been referred to previously. Biesele (40) observed more pepsin-digestible protein in chromosomes of leukemic, than in normal lymphocytes. Dustin (41) reported some conversion of desoxyribose nucleic acid into ribose nucleic acid during phagocytosis of lymphocyte nuclei within macrophages. Thorell (42) has published a monograph which includes data obtained from application of the ultraviolet techniques of Caspersson and his colleagues to a study of protein synthesis in the cells of lymphatic leukemia. The studies by Andreasen & Ottesen (28), showing a high rate of nucleic acid turnover in lymphoid tissue, were referred to previously. The increased basophilia seen by Dougherty & White (43) in the cytoplasm of lymphocytes following a single injection of pituitary adrenotrophic hormone or adrenal cortical extract has been shown by Dougherty, Lavin & White (44) to be due to the presence of an increased concentration of substances which absorb ultraviolet light at a wave length characteristic of nucleic acids and nucleoproteins. This increase of cytoplasmic nucleic acids and nucleoproteins observed in lymphocytes following augmentation of circulating adrenal cortical steroids is similar to that described by Bing,

Fagraeus & Thorell (45) in rabbits injected with polyvalent pneumococcal vaccine or horse serum. Wislocki & Dempsey (46) reported a loss of cytoplasmic basophilia from lymphocytes of lymphoid tissue sections incubated with ribonuclease.

Moolten (47) prepared from the spleen two steroid fractions, one causing a decrease in blood platelets, the other an increase. Splenic extracts which inhibited coagulation of oxalated blood by certain cultures of staphylococci were reported by Mercier, Pillet & Defosse (48). Thiersch (49) found that the histamine content of spleen and lymph nodes was normal in cases of monocytic leukemia. Ungar (50) has described the isolation of two substances from spleen, which have antagonistic actions on bleeding time, capillary permeability, and red cell hemolysis.

Several enzyme systems of lymphoid cells have been studied. In a wide variety of malignancies, Fishman & Anlyan (51) found a marked increase in the β-glucuronidase content of metastases-containing, as compared to uninvolved, lymph nodes. Merten (52) reported strong D-peptidase activity in lymphocytes from patients with lymphatic leukemia. The presence in lymphocytes of a peptidase which hydrolyzes leucylglycylglycine was indicated by the work of Holman, White & Fruton (53). This enzyme has been purified appreciably and its specificity studied by Fruton, Smith & Driscoll (54). Brauer & Hardenbergh (9) found little evidence for cholinesterase production in lymph nodes or lymphocytes. Wislocki & Dempsey (46) found that at pH 9.5, each of the three substrates, glycerophosphate, yeast nucleic acid, and fructose diphosphate, was hydrolyzed in the presence of sections of both spleen and lymph nodes. Mustard gas inhibited the anaerobic glycolysis of spleen in experiments described by Needham, Cohen & Barrett (55); obvious cell damage was present. On the other hand, Barron and co-workers (56) found that while nitrogen mustards, in concentrations below the LD_{50} for the rabbit, inhibited markedly the respiration of rabbit lymph nodes *in vitro*, there was little effect on anaerobic glycolysis.

Lowry and co-workers (57) reported that the ascorbic acid content of leukocytes appears to be a valid index of the body concentration of this vitamin. Wagner (58, 59), using a microquantitative method, found that glycogen present in white cells was restricted to granulocytes; no glycogen was detected in lymphocytes, either normal or leukemic. This is in agreement with the histo-

chemical evidence of Wislocki & Dempsey (46), who also reported that lymphocytes failed to show Sudan black staining for lipids. Limitations of this technique are suggested from analyses by Szego & White (60) which indicate 6 to 8 per cent of total lipid in lymphoid tissue. It is of interest to note that liver tissue with a similar lipid content also does not stain with Sudan black (60).

Factors Affecting the Structure and Size of Lymphoid Tissue

Nutritional factors.—Involution of lymphoid tissue as a result of partial or total inanition is a well-established observation. Inasmuch as inanition is one of the so-called nonspecific stimuli which augment pituitary-adrenal cortical secretion, White & Dougherty (61) examined the possible role of this endocrine mechanism in the lymphoid tissue involution produced by fasting. Whereas normal mice lost 40 per cent of their lymphoid tissue mass and nitrogen content during a forty-eight-hour fast, adrenalectomized mice showed no significant decrease of lymphoid tissue weight or nitrogen content during a similar fasting period. Actually under these experimental conditions there was a significant increase in lymphoid tissue weight and nitrogen content in the adrenalectomized mouse. These results led Homburger (62) to suggest an adrenal influence as possible explanation for the hyperplasia and increased nitrogen content of lymph nodes found in mice bearing the transplantable sarcoma 180. The increase in lymphoid tissue nitrogen in fasted, adrenalectomized, as compared to normal, mice has been confirmed recently by Szego & White (60) and by White, Hoberman & Szego (63), using isotopic nitrogen. In acutely starved rats, Cameron & Carmichael (64) observed a more rapid decrease in spleen weight than in the weight of kidneys, heart, and gonads. Quimby (65) also found that chronic starvation of thirty or ninety days' duration in young male rats decreased the relative weights of thymus and spleen. Refeeding did not restore spleen weight in proportion to body weight gain; the thymus, however, showed a relative hypertrophy.

The involution of lymphoid tissue described by Stoerk & Zucker (66) and Stoerk (67) in rats fed a pyridoxine-deficient diet led Stoerk (68) to demonstrate that lymphosarcoma implants failed to take, and established tumor transplants were caused to regress, by administration of desoxypyridoxine when the pyridoxine

content of the diet was low. Mushett, Stebbins & Barton (69) described a marked atrophy of spleen, thymus, and lymph nodes in chicks, puppies, and monkeys fed desoxypyridoxine. The most striking change in chicks was a failure of development of lymphoid elements in the spleen. The involution of lymphoid tissue induced by pyridoxine deficiency was not altered significantly in the absence of the adrenals, according to Stoerk (70). This is in harmony with the observations of Deane & Shaw (71) that although acute thymic involution occurred in pyridoxine-deficient rats, histochemical study revealed only transitory stimulation of the adrenal cortex. Similar findings were present in riboflavin-deficient rats, whereas thiamine deficiency caused marked stimulation of the zona fasciculata of the adrenal cortex with the expected thymic involution.

Severe atrophy of the thymus of paired-fed rats given a synthetic diet lacking in either phenylalanine or leucine was observed by Maun, Cahill & Davis (72, 73). White, White & Mider (74) have summarized their investigations showing that restriction of dietary cystine caused reduction of the incidence of methylcholanthrene-induced leukemia in CBA mice from 92.1 per cent (control diet) to 55 per cent (cystine-deficient diet). On the other hand, limitation of dietary lysine and tryptophane, while producing similar growth rate inhibition, did not decrease significantly the incidence of leukemia.

Age changes in lymphoid tissue.—Denz (75) has traced the histological changes in human lymph nodes from infancy to senility. Lymph nodes from both healthy and sick individuals showed age change differences related to their function and anatomical position; the histological alterations are described in detail. Andrew (76) and Andrew & Andrew (77) found that age changes in the spleens and deep cervical lymph nodes of one hundred Wistar rats were great enough to permit histological identification of nodes from young, middle-aged, and senile animals. Evidence was obtained in support of the concept that the lymphocyte is a multipotential, undifferentiated cell. The origin of lymph nodes was described as consisting primarily of a heaping up of undifferentiated mesenchymal cells, a process seen initially in the sequence of events described by Furuta (78) in the regeneration of nodes. Reinhardt (79) followed the weight of thymus, spleen, cervical and mesenteric lymph nodes in several hundred male and female rats

(Long-Evans strain) from birth to nineteen months of age. Maximum weight of the various tissues was attained in the following order: thymus, forty to sixty days of age; mesenteric lymph node, sixty-five days of age; and spleen and cervical nodes, one hundred days of age. With further age increase, the thymus underwent rather complete involution; the other tissues remained relatively constant in weight. It would appear that the tissues studied show a rapid weight increase during the period of most active increase in body weight and the attainment of sexual maturity.

Pituitary-adrenal cortical secretion.—In 1946, Cope & Rosenfeld (1) reviewed studies related to pituitary-adrenal cortical control of the physiological activity of the lymphocyte. Additional reviews have appeared by White & Dougherty (80) and Dougherty & White (81). The data led to the suggestion that the lymphocyte is an end cell of the action of the 11-oxygenated adrenal cortical steroids, as a consequence of which a wide variety of alterations occur in lymphocyte structure and function. Interpretation of the extensive recent literature dealing with the effects of pituitary-adrenal cortical secretion on lymphoid tissue is made difficult by a lack of distinction between the effects of a single dose of hormone as compared with the results of chronic dosage and because of inadequate information regarding variables, other than adrenal cortical steroids, which may affect lymphoid tissue.

Although Dougherty & White found that a single injection of pituitary adrenotrophic hormone or adrenal cortical extracts caused an acute dissolution of lymphocytes within lymphoid structures (82), these investigators observed (83) that daily adrenotrophic hormone administration in mice may give a variable histological picture. There was an initial dissolution of lymphocytes followed, despite continued hormone injection, by hyperplasia of lymph nodes. Subsequently, this cyclic histological picture (lymphocyte dissolution followed by lymph node hyperplasia) was repeated at regular intervals for approximately sixteen weeks, at which time the animals became refractory to further hormone injections. This refractory state was shown by Chase (84) to be characterized by the appearance of circulating antibodies to the adrenotrophic hormone. Yoffey & Baxter (85) found that whereas daily injection of adrenotrophic hormone in rats caused regressive changes in lymph nodes and thymus, daily administration of aqueous adrenal cortical extract caused a slight

but definite lymphoid tissue hyperplasia. Simonnet (86) confirmed the reported thymic involution following injection of adrenotrophic hormone or adrenal cortical extract. Desoxycorticosterone acetate did not alter thymic weight. The role of pituitary-adrenal cortical secretion in the regulation of lymphoid tissue size is seen in observations of White & Dougherty (61) that the lymphoid tissue involution of fasting did not occur in the absence of the adrenals. Grégoire (87) suggested that this endocrine mechanism mediates the thymic involution which persists during suckling since thymic regeneration, which occurred when suckling was stopped, and the maintenance of the involution during suckling, were both found to take place in spayed rats and were therefore independent of ovarian secretions. All groups of rats nursing young were found to have larger than normal adrenals. The results augment the large body of evidence that neurohumoral factors affect the secretory rates of pituitary hormones, probably including adrenotrophin. The neurohumoral aspects of anterior hypophyseal secretory activity have been reviewed recently by Friedgood (88) and by Harris (89).

The *in vivo* lymphocytolysis caused by pituitary-adrenal cortical secretion has led to efforts to duplicate this phenomenon *in vitro*. Robertson (90) was unable to demonstrate a direct lytic action of adrenal cortical extract on lymphocytes *in vitro*. On the other hand, Heilman (91) observed an increase in the rate of degeneration of small and medium-sized lymphocytes in tissue culture as a result of the addition to the culture of 11-dehydro-17-hydroxycorticosterone or 11-dehydrocorticosterone. Production of an *in vivo* lymphocytolysis by adrenal cortical extract has been reported recently by Hechter & Stone (92) and by Schrek (93). The latter author also found that desoxycorticosterone acetate, adrenotrophic hormone, or various sex hormones were without effect under his experimental conditions. However, Dontigny (94) produced thymic atrophy in rats by injection of large doses of desoxycorticosterone acetate. Moreover, this effect could be obtained in adrenalectomized rats. A total of 20 mg. of the steroid was given in a two-day period. The involution was limited to the thymus and was not evident in lymph nodes.

Law & Speirs (95) examined the possible lymphocytolysis of malignant lymphocytes *in vivo* by injecting a lipoadrenal cortical extract (Upjohn) twice daily for forty-eight hours into mice of the

inbred C58 and RIL strains in the terminal stages of leukemia. Regression of infiltrated thymuses and subcutaneous lymph nodes was reported, with extensive pyknosis, dissolution, and depletion of lymphocytes in lymphoid tissue. Dougherty & White (83) saw no regression of a transplantable lymphosarcoma in CBA mice given daily injections of either adrenotrophic hormone or adrenal cortical extracts. A slight delay in tumor growth rate was observed if hormone administration was begun at the time of transplant inoculation. Also, administration of adrenal cortical steroids in oil (Upjohn) did not prolong the life of mice of the F strain (Strong) in which clinical evidence of leukemia was present.

Sex hormones.—Andreasen (29) studied the influence of endogenous sex hormones on lymphoid tissue size by comparing lymphoid tissue weights in both sexes of young mature guinea pigs; the total amount of lymph nodes and splenic lymphatic tissue was greater in females. The sex difference was most pronounced for the thymus, in which it amounted to 54 per cent, as compared to 24 per cent for the spleen and 23 per cent for the lymph nodes. Body weights and weights of the liver and kidneys were the same in the two sexes. Administration of massive doses of estradiol propionate to rats was reported by Plagge (96) to produce extensive epithelial cords and cysts in the thymus after ten months' treatment. There was no indication of carcinoma. Dmochowski & Horning (97) observed changes in lymphoid tissue varying from a simple enlargement to hyperplasia with invasion of surrounding tissues as a result of painting both castrated and noncastrated male mice with a chloroform solution of estrone. Histologically, the changes resembled neoplasia, but transplantation was unsuccessful. Cameron, Guthrie & Carmichael (98) caused reduction in spleen size in rats by oral administration of estradiol or stilbestrol. Adrenal enlargement was seen frequently. Clavert (99) found that estradiol propionate injection in pigeons also caused splenic pulp atrophy, a marked destruction of lymphocytes, and an increase in macrophages.

In further studies of interrelationships between the sex glands and lymphoid tissue, Plagge (100) reported that experimental cryptorchidism (abdominal confinement of the testes) produced no significant weight change in either thymus or lymph nodes, whereas castration caused a highly significant enlargement of lymphoid structures (mediastinal). Simonnet (86) observed marked thymic

involution in rats injected with an aqueous, testicular extract, and Quimby (65) found that testosterone injections in rats recovering from chronic starvation prevented restoration of weight of the involuted thymus. Biesele & Gasic (101) concluded that although testosterone propionate pellets diminished chromosome size of normal lymphocytes, the hormone had no effect on the chromosomes of leukemic cells.

Growth hormone.—Szego & White (60) found that injection of a very large dose (4 mg.) of purified anterior pituitary growth hormone [Fishman, Wilhelmi & Russell (102)] into mice during a forty-eight-hour fast exaggerated the lymphoid tissue involution of fasting. However, this was probably due to nonspecific augmentation of pituitary-adrenal cortical secretion, since injection of a smaller dose of growth hormone (200 μg.) into either intact or adrenalectomized mice did not accentuate lymphoid tissue involution. The lymphoid tissue in all fasting animals showed a disproportionately large loss of lipid, as compared to losses in other constituents. The lipid content of the lymphoid tissue declined even in fasted, adrenalectomized mice which, at the same time, were increasing the weight and nitrogen content of their lymphoid structures.

Radiant Energy, Chemical and Physical Agents as Stimuli

Many physical and chemical agents cause exaggeration of normal physiological relationships between the lymphatic organs and pituitary-adrenal cortical secretion (103) as a consequence of their augmentation of the release of adrenotrophic hormone (104). It is not surprising, therefore, that a wide variety of physical and chemical stimuli have been reported to affect lymphoid tissue size and structure.

Radiant energy.—Radiant energy of varying wave lengths has marked effects on lymphoid tissue. Dougherty & White (105) have confirmed the conclusions of Leblond & Segal (106) that a portion of the general involution of lymphoid tissue seen following exposure to total body x-radiation is mediated by the pituitary-adrenal cortical mechanism. The observation (105) that x-radiation augments pituitary-adrenal cortical secretion in mice, as judged by adrenal cholesterol analyses, has been confirmed in rats by Patt

and his co-workers (107). In a series of papers, Schrek (108 to 112) has applied his methods of unstained cell counts and dark field microscopy to studies of the sensitivity of lymphocytes to x-radiation *in vitro*. X-radiation was observed to accelerate greatly the production of vacuoles which appear normally in lymphocytes during their incubation. A radiation dose of 50 r appeared to be minimum for significant alteration *in vitro* of lymphocyte viability. Radiation under anaerobic, in contrast to aerobic, conditions produced no perceptible alterations in lymphocytes. Dickie & Hempelmann (113) examined supravital preparations of blood cells of persons chronically exposed to ionizing radiations and toxic chemicals and found that the cytoplasm of blood lymphocytes showed a striking increase in the number of refractive, neutral red bodies.

Chemical agents.—Several groups of chemical compounds have been studied with respect to their effects on normal, as well as malignant, lymphoid tissue. Extensive work has been done particularly with the so-called nitrogen mustards [(bis- and tris-[2-dichloroethyl]methylamine hydrochlorides)], the sulfur mustard [(bis[2-chloroethyl]sulfide)], and urethane. Kindred (114) described in detail the influence of certain nitrogen and sulfur mustards, given intravenously in lethal doses, on the size and structure of lymphoid organs of rats. A marked reduction occurred in the weight of lymphoid tissues, with destruction of lymphocytes and inhibition of mitosis. The reticulum cells of the lymphoid organs did not appear to be injured directly by the agents and, as fixed phagocytes, were engaged actively in the digestion of degenerated lymphocytes. Similar results were obtained in adrenalectomized rats; hence the action of these agents is not necessarily pituitary-adrenal cortical mediated. However, the nitrogen and sulfur mustards do augment pituitary-adrenal cortical secretion in rats, as judged by adrenal weight and cholesterol data of Ludewig & Chanutin (115, 116). Therefore, in intact animals there could be both a direct and indirect effect of these toxic chemicals. Similar reduction in weight and cell numbers of lymphoid organs, following treatment with nitrogen or sulfur mustards, have been reported in laboratory animals by other investigators (117, 118, 119). The clinical response of malignant lymphoid tissue to these chemical agents has been summarized and evaluated recently by Craver

(120). Limitation of space does not permit discussion of numerous studies of the action of nitrogen and sulfur mustards on malignant lymphoid tissue.

The effects of urethane on normal lymphoid cells have also been studied in a number of laboratories, generally as incidental to studies of the influence of this chemical on experimental and clinical leukemias. In general, urethane therapy in either spontaneous or transplantable lymphatic leukemia resulted in a decrease in the size of subcutaneous lymph nodes, spleen, and thymus (121 to 126). Berman & Axelrod (127) have reviewed recently some of the literature concerned with the chemotherapeutic studes of urethane in malignant disease. It is of interest that the alterations in lymphoid structures seen following urethane are similar to those reported following injection of pituitary adrenotrophic or adrenal cortical hormones (82), i.e., marked pyknosis of lymphocyte nuclei, and karyolysis and karyorrhexis of lymphocytes. However, the recent work of Dury & Robin (128), using blood lymphocyte levels as the criterion for interpretation, indicates that urethane may exert an influence on lymphocytes which is not mediated by the adrenal cortex. The lymphopenia seen in adrenalectomized rats injected with urethane was probably due to inhibition of mitosis in lymphocytes.

Burmester (129) described a cytotoxic activity of serum of lymphoid tumor-immune chickens which was manifested by an *in vitro* and *in vivo* toxic action upon lymphoid tumor cells. *In vitro* lysis of lymphocytes from tuberculous humans by tuberculoprotein was reported by Fremont-Smith & Favour (130), extending an earlier observation by Favour (131) that lymphocytes from animals infected with certain bacteria are specifically destroyed by contact, *in vitro*, with protein extracts of these bacteria. Grégoire (132) observed thymic involution in rats given 0.1 per cent of aminothiazole for three weeks in drinking water.

Physical stimuli.—Latta & Nelson (133) found that rats subjected to hyperpyrexia and/or physical restraint (tying on an animal board) showed a relative depletion of small lymphocytes in all lymph nodes with a marked increase in the number of macrophages. The possible influence of these stimuli on augmentation of pituitary-adrenal cortical secretion was apparently not considered in evaluating the data, although these stimuli produce increased activity of this endocrine mechanism (134, 135). This may explain

in part the similarity of the histological responses described by Latta & Nelson (133) for both types of stress.

In concluding this consideration of the influence of a variety of factors on the size and structure of lymphoid tissue, a few comments appear in order regarding distinctions made in the literature between a pituitary-adrenal cortical-mediated, as compared to a direct action on lymphoid tissue. The data indicate that some stimuli, e.g., cold, heat, inanition, epinephrine, histamine, etc., alter lymphoid tissue physiology in the intact organism only, while others, e.g., nitrogen mustards and large doses of certain hormones, may induce these changes in the adrenalectomized or hypophysectomized animal. The former response has been described as an indirect endocrine-mediated one, while the latter, occurring in the absence of adrenals or hypophysis, has been termed a direct response of lymphoid tissue to the stimulus. X-radiation elicits both types of actions. The compartmentalization of the stimuli into indirect, as contrasted to direct, would appear undesirable. Toxic agents which induce involution of lymphoid tissue in adrenalectomized or hypophysectomized animals must also augment pituitary-adrenal cortical secretion in the intact organism. This is the case apparently for the nitrogen mustards. Conversely, stimuli which alter lymphoid tissue only in the presence of the endocrine mechanism may also, if increased in intensity, produce lymphoid tissue changes in the adrenalectomized or hypophysectomized organism, provided the increased susceptibility of the latter to the stress does not result in early death. Inanition or estrogens are examples of this circumstance. It is not unlikely that a variety of mechanisms participate in regulation of lymphoid tissue physiology, and it would seem undesirable to attempt to explain the diverse results caused by a variety of stimuli on the basis of a single, restricted mechanism or process.

Blood Lymphocyte Levels

The demonstration (136, 137) that pituitary-adrenal cortical secretion influences the level of blood lymphocytes has been confirmed in a number of laboratories in studies of lymphocyte counts in blood and thoracic duct lymph. An acute lymphopenic response following adrenotrophic hormone or adrenal cortical extract injection was reported in rats by Reinhardt & Li (138) and Simonnet (86), in dogs by Reinhardt, Aron & Li (139), in cats and

rats by Yoffey, Reiss & Baxter (140) and Yoffey & Baxter (85), and in human subjects by Pincus (141), Forsham and co-workers (142), Hills, Forsham & Finch (143), Hellman and co-workers (144), Darrow (145), and Adams (146). On the other hand, Valentine, Craddock & Lawrence (147) did not observe a lymphopenia in the thoracic duct lymph or the blood of cats injected with adrenal cortical extract. Also, Kelley & Adams (148) found no change in the blood picture of children given single injections of aqueous adrenal cortical extracts, and Mason and co-workers (149) reported that chronic injections of adrenotrophic hormone in a human subject did not alter blood lymphocyte levels. Kelley & Adams (148) pointed out that the dose of hormone employed (5 to 8.5 ml.) may have been too small. Mason and co-workers (149) do not, with one exception, indicate the time at which blood was examined during the experimental periods. It should be pointed out that in both animals and man, the lymphopenic response to adrenotrophic hormone or adrenal cortical extract is an acute one, generally maximal at three to six hours after hormone injection, with a rapid return to normal lymphocyte levels in the blood. This acute change, with restoration to normal values in a few hours, was found by Dougherty & White (83) to be reproduced each day for twelve weeks in mice given daily injections of adrenotrophic hormone. In view of the statement by Mason and co-workers (149) that only a single lymphopenic effect was observed in the subject on the twenty-second day of hormone administration and "the effect lasted less than three hours," it would be important to know at what precise intervals during their experimental period blood was drawn for lymphocyte determinations.

Malméjac, Chardon & Gross (150) produced an acute lymphopenia in dogs by intravenous injection of epinephrine, a potent activator of the pituitary-adrenal cortical mechanism (151). Epinephrine had no lymphopenic action in adrenalectomized dogs. In cross-circulation experiments, injection of epinephrine in one dog produced a lymphopenia in the other.

Hechter (152) has induced a prompt discharge of splenic lymphocytes *in vitro* by addition of adrenal cortical extract to whole blood perfused through rabbit spleen. Stone & Hechter (153) further implicated the spleen as a source of blood lymphocytes by showing that the lymphocytosis seen in rats exposed to stress (swimming) was decreased either by adrenalectomy or splenectomy. Adrenal

cortical extract, but not desoxycorticosterone acetate, administered to swimming adrenalectomized rats produced lymphocytosis, but had no effect on blood lymphocyte levels when given to swimming, adrenalectomized-splenectomized animals. These observations suggested that adrenal cortical extract causes splenic lymphocyte discharge.

The variety of toxic chemicals (nitrogen and sulfur mustards, urethane, desoxypyridoxine) discussed previously in relation to their effects on lymphoid tissue size and structure also produced, in many of the studies cited, a lymphopenia. Dury & Robin (128) suggested that urethane acts directly on lymphocytes as a mitotic poison, inasmuch as the absolute lymphopenia seen in normal rats following five or six intraperitoneal injections of urethane can be reproduced in adrenalectomized animals. The authors may have overlooked a possible acute effect on blood lymphocytes which could be an adrenal-mediated process, since the first blood sample was taken only at the end of the first week, after three injections of urethane.

The well-known lymphopenic effect of x-radiation was studied by Dougherty & White (105), who concluded that a portion of the changes in lymphocyte physiology which were seen is mediated via the pituitary-adrenal cortical mechanism. The data obtained by Lawrence, Valentine & Dowdy (154) indicated to those authors that there was no specific, indirect action of x-rays which was uniquely characteristic for x-radiation only. Jacobson & Marks (155) believe that lymphocyte reduction in the peripheral blood is the most sensitive indicator of acute or subacute exposure to externally ionizing radiation or internally deposited radioisotopes.

The lymphocytopenia of stress has received attention because of an apparent difference in response between certain categories of psychotics, on the one hand, and other groups of individuals. These studies have been based on the observations by Pincus and co-workers (135, 156) that the lymphopenia seen in mice subjected to stress (tying down on a wire grid or cold exposure), or in rats following oral glucose administration, did not occur in the absence of the adrenals. Using glucose administration and heat stress as experimental tools, Pincus and co-workers (141) have accumulated data which suggest that there is a lesser degree of lymphopenic response in psychotic than in normal subjects. However, injection of adrenotrophic hormone in psychotics produced marked lympho-

penia, indicating adequate reaction of the patients' adrenal glands to the normal physiological stimulant. It would appear that the impaired adrenocortical response of certain psychotics to stress is concerned with the mechanism regulating secretion of adrenotrophic hormone by the anterior pituitary gland. The nature of this mechanism remains to be elucidated.

In view of the foregoing, it is surprising that Latta & Nelson (133) failed to consider pituitary-adrenal cortical secretion as a factor in the severe, acute lymphopenia they observed in rats subjected to restraint (tying on an animal board) and/or hyperpyrexia. Mikkelsen & Hutchens (157) reported recently that a significant lymphopenia was found on the third hour following electric shock therapy in male psychotic patients and related the data to the pituitary-adrenal cortical influenced lymphopenia of stress.

Harris & Henle (158) observed a striking lymphopenia within three hours after intravenous injection in rabbits of allantoic fluid infected with viruses of influenza Types A or B, or of the virus particle separated by centrifugation. The response was type-specifically neutralized by rabbit immune serum. A similar lymphopenia was obtained by injection of the virus of mumps, rough pneumococci, and nucleoproteins derived from hemolytic streptococci. Control rabbits injected with normal allantoic fluid, horse blood, or immune or normal rabbit sera showed no lymphopenia. Injection of antigens or acetylcholine into human subjects has been reported by Danielopolu and co-workers (159) to produce lymphopenia.

Andreasen & Gottlieb (160) subjected rats to subtotal, extensive lymphadenectomy and found an early, profound, absolute lymphopenia which was due to operative stress, since control, sham-operated rats responded in a similar manner. The blood lymphocyte level tended to remain at lower than normal values for several weeks in the animals with a reduced mass of lymphoid tissue. However, normal blood lymphocyte levels were re-established three to six weeks after lymphoid tissue extirpation, although at necropsy there was no evidence of regeneration of the lymphoid structures. This last observation remains unexplained. Reinhardt (79) contributed to the problem of factors influencing numbers of blood lymphocytes by studying the rate of delivery of these cells into the blood stream in thirty-three adult female rats by

cannulation and collection of lymph from cervical and thoracic ducts. Delivery of lymphocytes into the blood per hour was calculated as being approximately 10 per cent of the number present in the blood and is adequate to replace blood lymphocytes twice each twenty-four hours. The calculated average duration of the lymphocyte in the blood stream of the rat was thus approximately twelve hours.

A critical analysis of the literature relating to pituitary-adrenal cortical control of lymphoid tissue structure and function and of the numbers of blood lymphocytes has been prepared recently by Valentine, Craddock & Lawrence (147).

Relation of Lymphoid Tissue to Normal and Immune Globulin Production

Ehrich (161) and White & Dougherty (80) have reviewed the role of lymphoid tissue in normal and immune globulin production. The recent investigations in this field have been concerned with blood levels of normal and immune globulins, and the site and mechanism of antibody production.

Blood globulins.—Attempts to confirm the observation that a single injection of adrenotrophic hormone or adrenal cortical extract produces a rise in blood globulins (86, 162) have yielded diverse results. It would appear that a number of variables may affect possible relations of pituitary-adrenal cortical secretion, or of activators of this mechanism, to the level of circulating blood globulins. Simonnet (86), working with rats, has confirmed the increase in blood globulin reported following injection of adrenotrophic hormone or adrenal cortical extracts and concluded that the two-month-old male rat was the most responsive animal. This investigator also confirmed the failure of desoxycorticosterone acetate to influence blood globulin concentrations. On the other hand, Li & Reinhardt (163) could not alter the electrophoretic serum protein pattern of normal or hypophysectomized rats by giving single or chronic injections of adrenotrophic hormone. Milne & White (164) have also failed to obtain consistent changes in the globulin fractions of the serum proteins of rats examined three to six hours following subcutaneous injection of large doses of adrenal cortical steroids in oil. It appeared that the previous dietary history of the animals may have been a significant variable. The marked influence of nutritional factors on serum globulin

production is illustrated in the work of Cannon, Chase & Wissler (165).

In rats and dogs exposed to physical and chemical stimuli which augment pituitary-adrenal cortical secretion, Chanutin and co-workers (166, 167) observed rather uniformly an increase in the serum α-globulin fractions, the appearance of boundary anomalies in the β-globulin component, and a decrease in total albumin concentration. Indeed, three α-globulin rich fractions, not present in detectable amounts in the sera of normal dogs, were separated by Gjessing, Ludewig & Chanutin (167) from the sera of injured dogs. It is unlikely that these proteins originated from a single histological structure, in view of the generalized tissue injury and trauma induced by the injurious agents (turpentine, heat, and sulfide mustard) used.

An increase in serum globulins was reported by Arocha & De Venanzi (168) following intravenous injection of adrenal cortical extract in normal but not in splenectomized dogs. This is in accord with Benhamou & Gille (169), who found a rise in blood globulins in dogs and human subjects after intravenous epinephrine, but no increase under similar circumstances in splenectomized dogs or humans. Mondolfo & De Lerner (170) confirmed the report of Chase, White & Dougherty (171) that adrenal cortical extract injections accompanying antigen administration result in a greater rate and degree of elevation of blood immune globulins. However, Eisen and co-workers (172) found identical concentrations of serum antibodies and γ-globulin in adrenalectomized rats injected repeatedly during immunization with adrenal cortical extract, and in operated animals not receiving hormone. Of interest was the observation of Mondolfo & De Lerner (170) that very large doses of adrenal cortical extract may suppress the rate of antibody formation. Danielopolu and co-workers (159) found that injection of eserine or strophanthin increased serum globulin concentrations.

Pituitary adrenotrophic hormone or adrenal cortical extract injections have failed generally to influence the level of serum globulins in human subjects. This has been the experience of Kelley & Adams (148), Forsham and co-workers (142), Mason and co-workers (149), and Frieden & White (173), following administration of adrenotrophic hormone or adrenal cortical extracts. Moreover, exposure of patients to x-radiation, nitrogen mustard therapy, or electric shock treatment was rather uniformly without influence

on the electrophoretic serum protein pattern, although in two instances significant rises were seen in the serum γ-globulin fraction after x-radiation (173).

Stoerk, John & Eisen (174), using glycine containing isotopic nitrogen as a labelling agent, found that the rate of turnover of serum proteins of rats was unaffected by adrenalectomy or by administration of adrenal cortical steroids to adrenalectomized animals. These data are in contrast to the recent findings of White, Hoberman & Szego (63), who also used N^{15} labelled glycine to examine the rate of nitrogen turnover in tissues. Adrenalectomized mice fasted for a sixty-six-hour period had significantly higher concentrations of isotope in the total proteins of spleen, thymus and lymph nodes, and serum, than did intact, fed mice, or unoperated mice also fasted for sixty-six hours. The absence of the adrenals did affect markedly the net rate of turnover of these tissue proteins, including the total serum proteins. There was no significant difference in isotope content of the total proteins of liver, gut, or kidney in operated as compared to intact, fasted mice. It is of some interest that all groups of fasted mice had a higher isotope concentration in their tissue proteins than was present in the proteins of comparable structures of the intact, fed group of controls. The data suggest a depression of protein turnover rate, including the proteins of lymphoid tissue, as a result of fasting, as well as of adrenalectomy.

Site and Mechanism of Antibody Production

The anamnestic response.—The data of Dougherty, Chase & White (175) led those authors to postulate that pituitary-adrenal cortical influence on the structure and function of lymphoid tissue is the normal physiological basis of the anamnestic response. In hyperimmunized rabbits, a single injection of adrenal cortical extract or of adrenotrophic hormone resulted within six hours in a rise in blood antibodies (171). Similarly, previously immunized rabbits, with no circulating antibody, showed significant antibody titers within a few hours following injection of hormone. Also, the anamnestic response seen in previously immunized mice following a single injection of benzene or sodium arsenite was not evident in the absence of the adrenals. It seems likely that these toxic chemicals caused, in the intact mice, an augmentation of pituitary-adrenal cortical secretion, since injection of adrenotrophic hormone

in the unoperated group of animals, or adrenal cortical extract in the adrenalectomized mice, produced a definite anamnestic reaction.

Murphy & Sturm (176) obtained evidence of augmentation of circulating antibodies in immunized, adrenalectomized rabbits injected with adrenal cortical extract, although Kelley & Adams (148) did not find an increase in pertussis titer in children given single injections of adrenal cortical extract.[1]

As might be expected, the intensity and duration of the stimulus may modify the anamnestic response. This is of particular significance if the stimulus alters the normal structure and function of antibody-producing lymphoid cells. Philips, Hopkins & Freeman (177), working with goats, and Spurr (178), using rabbits, have independently found that although nitrogen mustards have a marked lymphocytotoxic effect, these agents interfered with the anamnestic reaction. Philips, Hopkins & Freeman (177) observed that if the nitrogen mustard was injected before the stimulating dose of antigen, there was a significant, though delayed anamnestic response. These authors point out that whereas both nitrogen mustard and adrenal cortical secretion accelerate lymphoid tissue involution and the release of constituents of this tissue to the circulation, normal restoration of lymphoid elements does not occur in the presence of the amine mustard.

The lymphocyte and antibody production.—Dougherty, Chase & White (179) and Harris and co-workers (180) demonstrated the presence of antibody in tissue lymphocytes of immunized animals. This was confirmed by Mondolfo & Hounie (181). Unfortunately, these data have led the original investigators (179, 180) to be quoted erroneously as concluding that antibodies are formed in lymphocytes. The evidence that lymphocytes contain antibody need not necessarily mean that these cells produce immune globulin. If one accepts the derivation of lymphocytes from primitive reticulum and the evidence for the multipotentiality of this

[1] After this manuscript was in press, Dr. E. E. Fischel kindly permitted the author to see a forthcoming publication by Fischel, E. E., LeMay, M., and Kabat, E. A. These investigators, using the quantitative precipitin method, could not demonstrate an anamnestic rise in circulating antibody following administration of adrenotrophic hormone or x-ray to rabbits three months after cessation of immunization with crystalline egg albumin, even though there occurred a concomitant decrease in circulating lymphocytes.

cell, as reviewed by Bloom (182), lymphocytes need not manufacture antibody, and yet could contain the immune protein as a result of being derived from a cell type in which actual antibody synthesis occurred. Without this working hypothesis, it becomes difficult to visualize the formation of antibodies by mature lymphocytes which are nonphagocytic, unless lymphocytes can take up either preformed antibody or antibody-inciting material. Thus, Harris & Ehrich (183) postulated that particulate antigen is subjected to phagocytosis, which results in the liberation of smaller, soluble particles. These retain groupings immunologically characteristic of the original antigen and pass via the lymph into lymphatic tissue and, presumably, into lymphocytes where antibody synthesis takes place. However, Harris, Rhoads & Stokes (184), in *in vivo* studies, and Fagraeus (185) and Roberts, Adams & White (186), in *in vitro* experiments, could find no evidence of antibody production by the thymus, although this structure contains lymphocytes. Ehrich & Harris (187) and Ehrich (161) have reviewed the evidence for the lymphocytic theory of antibody formation.

Efforts to assess the role of the lymphocyte in immune globulin production have also been based on relating the size of lymphoid tissue to the level of blood antibody. It should be emphasized, however, that toxic agents which diminish lymphoid tissue mass may impair general tissue metabolism, and this could be an equally important influence on antibody formation. Decreased antibody formation accompanying lymphoid tissue destruction by x-radiation or nitrogen mustards does not establish unequivocally a causal relationship between the number of lymphocytes in lymphoid tissue and immune globulin formation. As further illustration, pyridoxine deficiency, which produces lymphoid tissue involution, was reported by Stoerk & Eisen (188) and Stoerk, Eisen & John (189) to depress antibody formation. A generalized impairment of protein synthesis in pyridoxine-deficient animals, could result in both antibody synthesis and new lymphocyte formation being depressed, quite independently of one another. Cannon, Chase & Wissler (165) demonstrated, for example, that impaired immune globulin synthesis is probably a special manifestation of a general deficiency in available dietary nitrogen for protein formation by all body cells. Also, a more generalized basis for the effect of pyridoxine deficiency on antibody formation is suggested from recent

observations by Axelrod and co-workers (190) and by Carter & Axelrod (191) that a variety of vitamin deficiencies other than pyridoxine, e.g., thiamine, biotin, and pantothenic acid, also impaired antibody synthesis.

The macrophage and antibody formation.—The classical experiments of Metchnikoff (192) on the relation of the phagocytic activity of the macrophage to immunity were extended in the careful study of Sabin (193), who concluded that cells of the reticuloendothelial system, notably macrophages, were concerned actively with antibody formation. Ehrich, Harris & Mertens (194) failed to find antibody in macrophages present in the peritoneal exudate of immunized rabbits and concluded that antibody was not produced by the macrophage. The time relations between injection of antigen and the stimulus to macrophage development may have been an important variable in these experiments.

Role of the plasma cell in antibody formation.—Fagraeus (195) has reviewed recently the hypothesis that hyperglobulinemia is a result of increased production of plasma cells. This postulate is based on observations by Bing & Christensen (196), Bing, Fagraeus & Thorell (45), Bjørneboe & Gormsen (197), Bjørneboe, Gormsen & Lundquist (198), and Fagraeus (185, 195) that antibody production was accompanied by an increased number of plasma cells in bone-marrow, spleen, and lymph nodes. Moreover, significant amounts of immune globulin were demonstrated in tissues of immunized animals in which large numbers of plasma cells were seen, e.g., adipose tissue of the renal sinus (198). Grégoire (199) has also described a marked increase in basophilic lymphocytes in the germinal centers of lymph nodes following injection of an antigen.

The possible relationship of true plasma cells to antibody formation is somewhat obscured by the common practice of designating any cell of the lymphoid series, having a basophilic cytoplasm, a "plasma cell." Moreover, while the demonstration of a relationship between numbers of plasma cells and antibody formation has been achieved *in vivo* in the experiments of Bjørneboe, Gormsen & Lundquist (198), and *in vitro* in the studies of Fagraeus (185, 195), one may still question whether the relationship is a causal one.

Site of antibody formation.—Fagraeus (185) found that following intravenous injection of antigen in a rabbit, the excised splenic tissue, studied in tissue culture, produced significant amounts of

antibody. Intravenous injection of live bacteria or an azoprotein showed approximately equal distribution of the injected material between spleen and liver, with little in lymph nodes and thymus. After subcutaneous injection, antigen could be seen in large amounts in regional lymph nodes. These data are largely in agreement with those of Roberts, Adams & White (186), who studied antibody release by spleen, lymph node (mesenteric), or thymus obtained from immunized rats and incubated in nonimmune rat serum. When a single dose of antigen was given intravenously, antibody formation was highest in splenic tissue, less in mesenteric lymph node, and lacking in thymus. However, with multiple intraperitoneal injections of antigen, the only significant release of antibody occurred with mesenteric lymph node. Harris *et al.* (184) likewise observed that the thymus played no demonstrable role in the production of antibodies by the young rabbit. Libby & Madison (200) found 63 per cent of intravenously injected tobacco mosaic virus, labelled with radioactive phosphorus, in the livers of mice twenty-four hours after injection. Only 3 per cent of the radioactivity was present in the spleen. Although reticuloendothelial cells of the liver may play a role in antibody formation, Roberts, Adams & White (201) found no evidence of antibody release by incubating liver tissue obtained from immunized rats, even though relatively high titers were demonstrable in liver extracts prior to incubation.

There has as yet been no demonstration of the precise cell type in which the first synthesis of immune globulin occurs following an injection of antigen. It would appear that antibody formation may be a generalized phenomenon of cells of the reticuloendothelial system. Whether the first modified globulin molecule is made in the primitive reticulum cell, or in cells differentiating therefrom, remains to be disclosed by future investigations. The delayed, but definite, anamnestic response seen by Philips, Hopkins & Freeman (177) in previously immunized goats, with no circulating antibody, and given chronic injections of nitrogen mustard before the stimulating dose of antigen, might be significant for this question. The delayed anamnestic response may have been a manifestation of temporary mitotic arrest of the lymphoid reticulum. Resumption of mitotic activity in relatively atrophic lymphoid tissue, with proliferation of the more primitive cells into mature antibody-containing lymphocytes, would account for the

delayed response and might indicate that the initial immunological reaction to the antigen occurs in the primitive lymphoid reticulum.

The appearance of large numbers of lymphocytes, with basophilic staining cytoplasm, at a time of active antibody formation, suggests that a causal relationship may exist between these cells and new globulin production. However, these cells, or similar ones, might increase in number in response to the presence of an excess of a foreign material, i.e., an antigen, for metabolic reasons unrelated to actual synthesis of new globulin. Finally, as is well known, the frequency and route of antigen injections may modify the antibody response. This would seem to be related to the question of the particular reticuloendothelial structure with which the antigen first comes in contact, and the specific reaction of this tissue to the foreign material.

LITERATURE CITED

1. COPE, O., AND ROSENFELD, L., *Ann. Rev. Physiol.*, **8**, 297–310 (1946)
2. DRINKER, C. K., AND HARDENBERGH, E., *J. Exptl. Med.*, **86**, 7–18 (1947)
3. CAMERON, G. R., AND COURTICE, F. C., *J. Physiol. (London)*, **105**, 175–85 (1946)
4. COURTICE, F. C., AND PHIPPS, P. J., *J. Physiol. (London)*, **105**, 186–90 (1946)
5. GILLMAN, T., AND IVY, A. C., *Gastroenterology*, **9**, 162–69 (1947)
6. PERRY, T. T., *Arch. Path.*, **43**, 456–65 (1947)
7. HAYNES, F. W., AND HARDENBERGH, E., *Am. J. Physiol.*, **146**, 666–72 (1946)
8. SALTER, W. T., *Western J. Surg., Obstet., and Gynecol.*, **55**, 15–26 (1947)
9. BRAUER, R. W., AND HARDENBERGH, E., *Am. J. Physiol.*, **150**, 746–53 (1947)
10. GONZALEZ-ODDONE, M. V., *Proc. Soc. Exptl. Biol. Med.*, **63**, 540–42 (1946)
11. LANDIS, E. M., *Ann. N. Y. Acad. Sci.*, **46**, 713–32 (1946)
12. MCMASTER, P. D., *Ann. N. Y. Acad. Sci.*, **46**, 743–88 (1946)
13. DRINKER, C. K., *Ann. N. Y. Acad. Sci.*, **46**, 807–22 (1946)
14. MIRSKY, A. E., AND POLLISTER, A. W., *J. Gen. Physiol.*, **30**, 117–48 (1946)
15. MIRSKY, A. E., AND RIS, H., *J. Gen. Physiol.*, **31**, 1–6 (1947)
16. MIRSKY, A. E., AND RIS, H., *J. Gen. Physiol.*, **31**, 7–18 (1947)
17. STERN, K. G., *Proc. Intern. Physiol. Congr., 17th Congr.*, 120 (1947)
18. EULER, H.v., FISCHER, I., HASSELQUIST, H., AND JAARMA, M., *Arkiv Kemi Mineral. Geol.*, [A]**21**(12), 1–15 (1946)
19. EULER, H.v., AND HÖGBERG, B., *Arkiv Kemi Mineral. Geol.* [A]**22**(9), 13 pp. (1946)
20. EULER, H.v., AND HAHN, L., *Arkiv Kemi Mineral. Geol.* [A]**22**(17), 14 pp. (1946)
21. ABRAMS, A., AND COHEN, P. P., *Federation Proc.*, **7**, 140 (1948)
22. ROBERTS, S., AND WHITE, A., *Federation Proc.*, **7**, 181 (1948)
23. PRAETORIUS, E., *Compt. rend. trav. lab. Carlsberg. Sérchim. physiol.*, **26**, 168–96 (1947)
24. KJERULF-JENSEN, K., *Proc. Soc. Exptl. Biol. Med.*, **66**, 624–25 (1947)
25. AHLSTROM, L., AND EULER, H.v., *Arkiv. Kemi. Mineral. Geol.* [A]**23**(3), 10 pp. (1946)
26. BLOOM, W. L., WATSON, D. W., CROMARTIE, W. J., AND FREED, M., *J. Infectious Diseases*, **80**, 41–52 (1947)
27. WEISSMAN, N., AND GRAF, L. H., *J. Infectious Diseases*, **80**, 145–53 (1947)
28. ANDREASEN, E., AND OTTESEN, J., *Acta Physiol. Scand.*, **10**, 258–70 (1945)
29. ANDREASEN, E., *Acta Anat.*, **1**, 359–64 (1946)
30. FURTH, J., *Physiol. Revs.*, **26**, 47–76 (1946)
31. KAPLAN, H. S., *Cancer Research*, **7**, 141–7 (1947)
32. COMSA, J., *Compt. rend. soc. biol.*, **139**, 1035–36 (1945)
33. DIAZ-GUERRERO, R., THOMSON, J. D., AND HINES, H. M., *Am. J. Physiol.*, **151**, 91–95 (1947)
34. STUTZ, V., AND VERZÁR, F., *Helv. Physiol. et Pharmacol. Acta*, **5**, 52–54 (1947)
35. TISSIÉRES, A., VOGT, O., AND VERZÁR, F., *Helv. Physiol. et Pharmacol. Acta*, **5**, 54–56 (1947)
36. CASTELLANOS, H., *Rev. soc. argentina biol.*, **23**, 51–55 (1947)
37. CASTELLANOS, H., *Rev. soc. argentina biol.*, **23**, 56–61 (1947)

38. CASTELLANOS, H., AND HOUSSAY, H. E. J., *Rev. soc. argentina biol.*, **23**, 96–98 (1947)
39. ANDREASEN, E., *Acta Anatomica*, **2**, 275–86 (1947)
40. BIESELE, J. J., *Cancer Research*, **7**, 70–77 (1947)
41. DUSTIN, P., JR., *Compt. rend. soc. biol.*, **140**, 910–11 (1946)
42. THORELL, B., *Acta Med. Scand.*, 129, Suppl. No. 200, 120 pp. (1947)
43. DOUGHERTY, T. F., AND WHITE, A., *Anat. Record*, **94**, 457–58 (1946)
44. DOUGHERTY, T. F., LAVIN, G. I., AND WHITE, A. (Unpublished data)
45. BING, J., FAGRAEUS, A., AND THORELL, B., *Acta Physiol. Scand.*, **10**, 282–95 (1945)
46. WISLOCKI, G. B., AND DEMPSEY, E. W., *Anat. Record*, **96**, 249–78 (1946)
47. MOOLTEN, S. E., *J. Mt. Sinai Hosp. N. Y.*, **12**, 866–73 (1945)
48. MERCIER, P., PILLET, J., AND DEFOSSE, G., *Compt. rend. soc. biol.* **141**, 139–40 (1947)
49. THIERSCH, J. B., *Australian J. Exptl. Biol. Med. Sci.*, **25**, 79–81 (1947)
50. UNGAR, G., *J. physiol.*, **39**, 219–48 (1947)
51. FISHMAN, W. H., AND ANLYAN, A. J., *J. Biol. Chem.*, **169**, 449–50 (1947)
52. MERTEN, R., *Biochem. Z.*, **318**, 185–97 (1947)
53. HOLMAN, H., WHITE, A., AND FRUTON, J. S., *Proc. Soc. Exptl. Biol. Med.*, **65**, 196–99 (1947)
54. FRUTON, J. S., SMITH, V. A., AND DRISCOLL, P. E., *J. Biol. Chem.*, **173**, 457–69, (1948)
55. NEEDHAM, D. M., COHEN, J. A., AND BARRETT, A. M., *Biochem. J.*, **41**, 631–39 (1947)
56. BARRON, E. S. G., BARTLETT, G. R., MILLER, Z. B., MEYER, J., AND SEEGMILLER, J. E., *J. Exptl. Med.*, **87**, 503–19 (1948)
57. LOWRY, O. H., BESSEY, O. A., BROCK, M. J., AND LOPEZ, J. A., *J. Biol. Chem.*, **166**, 111–19 (1946)
58. WAGNER, R., *Arch Biochem.*, **11**, 249–58 (1946)
59. WAGNER, R., *Blood*, **2**, 235–43 (1947)
60. SZEGO, C. M., AND WHITE, A., *Endocrinology* (In press)
61. WHITE, A., AND DOUGHERTY, T. F., *Endocrinology*, **41**, 230–42 (1947)
62. HOMBURGER, F., *Science*, **107**, 648–49 (1948)
63. WHITE, A., HOBERMAN, H. D., AND SZEGO, C. M., *J. Biol. Chem.*, **174**, 1049–50 (1948)
64. CAMERON, A. T., AND CARMICHAEL, J., *Can. J. Research* [E]**24**, 37–48 (1946)
65. QUIMBY, F. H., *Endocrinology*, **42**, 263–73 (1948)
66. STOERK, H. C., AND ZUCKER, T. F., *Proc. Soc. Exptl. Biol. Med.*, **56**, 151–53, (1944)
67. STOERK, H. C., *Proc. Soc. Exptl. Biol. Med.*, **62**, 90–96 (1946)
68. STOERK, H. C., *J. Biol. Chem.*, **171**, 437–38 (1947)
69. MUSHETT, C. W., STEBBINS, R. B., AND BARTON, M. N., *Trans. N. Y. Acad. Sci.*, **9**, 291–96 (1947)
70. STOERK, H. C., *Federation Proc.*, **7**, 281 (1948)
71. DEANE, H. W., AND SHAW, J. H., *J. Nutrition*, **34**, 1–15 (1947)
72. MAUN, M. E., CAHILL, W. M., AND DAVIS, R. M., *Arch. Path.*, **39**, 294–300 (1945)

73. MAUN, M. E., CAHILL, W. M., AND DAVIS, R. M., *Arch. Path.*, **40**, 173–78 (1945)
74. WHITE, J., WHITE, F. R., AND MIDER, G. B., *Ann. N. Y. Acad. Sci.*, **49**, 41–8 (1947)
75. DENZ, F. A., *J. Path. Bact.*, **59**, 575–91 (1947)
76. ANDREW, W., *Am. J. Anat.*, **79**, 1–74 (1946)
77. ANDREW, W., AND ANDREW, N. V., *Am. J. Anat.*, **82**, 105–66 (1948)
78. FURUTA, W. J., *Am. J. Anat.*, **80**, 437–506 (1947)
79. REINHARDT, W. O., *Anat. Record*, **94**, 197–211 (1946)
80. WHITE, A., AND DOUGHERTY, T. F., *Ann. N. Y. Acad. Sci.*, **46**, 859–82 (1946)
81. DOUGHERTY, T. F., AND WHITE, A., *J. Lab. Clin. Med.*, **32**, 584–605 (1947)
82. DOUGHERTY, T. F., AND WHITE, A., *Am. J. Anat.*, **77**, 81–116 (1945)
83. DOUGHERTY, T. F., AND WHITE, A., (Unpublished data)
84. CHASE, J. H. (Unpublished data)
85. YOFFEY, J. M., AND BAXTER, J. S., *J. Anat.*, **80**, 132–41 (1946)
86. SIMONNET, H., *Bull. acad. méd. (Paris)*, **131**, 245–48 (1947)
87. GRÉGOIRE, C., *J. Endocrinol.*, **5**, 68–87 (1947)
88. FRIEDGOOD, H. B., *Endocrine Function of the Hypophysis*, 211 pp. (Oxford University Press, New York, N. Y., 1946)
89. HARRIS, G. W., *Physiol. Revs.*, **28**, 139–80 (1948)
90. ROBERTSON, J. S., *Nature*, **161**, 814 (1948)
91. HEILMAN, D. H., *Proc. Staff Meetings Mayo Clinic*, **20**, 310–12 (1945)
92. HECHTER, O., AND STONE, D., *Federation Proc.*, **7**, 52 (1948)
93. SCHREK, R., (Personal communication, 1948)
94. DONTIGNY, P., *Proc. Soc. Exptl. Biol. Med.*, **63**, 248–50 (1946)
95. LAW, L. W., AND SPEIRS, R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 226–30 (1947)
96. PLAGGE, J. C., *Arch. Path.*, **42**, 598–606 (1946)
97. DMOCHOWSKI, L., AND HORNING, E. S., *J. Path. Bact.*, **59**, 307–12 (1947)
98. CAMERON, A. T., GUTHRIE, J. S., AND CARMICHAEL, J., *Can. J. Research* [E]**24**, 105–18 (1946)
99. CLAVERT, J., *Compt. rend. soc. biol.*, **140**, 1015–17 (1946)
100. PLAGGE, J. C., *Anat. Record*, **98**, 597–608 (1947)
101. BIESELE, J. J., AND GASIC, G., *Cancer Research*, **7**, 65–69 (1947)
102. FISHMAN, J. B., WILHELMI, A. E., AND RUSSELL, J. A., *Science*, **106**, 402 (1947)
103. SELYE, H., *J. Clin. Endocrinol.*, **6**, 117–230 (1946)
104. SAYERS, G., SAYERS, M. A., FRY, E. G., WHITE, A., AND LONG, C. N. H., *Yale J. Biol. and Med.*, **16**, 361–92 (1944)
105. DOUGHERTY, T. F., AND WHITE. A., *Endocrinology*, **39**, 370–85 (1946)
106. LEBLOND, C. P., AND SEGAL, G., *Am. J. Roentgenol. Radium Therapy*, **47**, 302–6 (1942)
107. PATT, H. M., SWIFT, M. N., TYREE, E. B., AND JOHN, E. S., *Am. J. Physiol.*, **150**, 480–87 (1947)
108. SCHREK, R., *Proc. Soc. Exptl. Biol. Med.*, **58**, 285–86 (1945)
109. SCHREK, R., *Radiology*, **46**, 395–410 (1946)
110. SCHREK, R., *J. Cellular Comp. Physiol.*, **28**, 277–304 (1946)
111. SCHREK, R., *Proc. Soc. Exptl. Biol. Med.*, **64**, 381–84 (1947)

112. SCHREK, R., *J. Cellular Comp. Physiol.*, **30**, 203–24 (1947)
113. DICKIE, A., AND HEMPELMANN, L. H., *J. Lab. Clin. Med.*, **32**, 1045–59 (1947)
114. KINDRED, J. E., *Arch. Path.*, **43**, 253–95 (1947)
115. LUDEWIG, S., AND CHANUTIN, A., *Endocrinology*, **38**, 376–84 (1946)
116. LUDEWIG, S., AND CHANUTIN, A., *Endocrinology*, **41**, 135–43 (1947)
117. CAMERON, G. R., COURTICE, F. C., AND JONES, R. P., *J. Path. Bact.*, **59**, 425–35 (1947)
118. GRAEF, I., KARNOFSKY, D. A., JAGER, V. B., KRICHESKY, B., AND SMITH, H. W., *Am. J. Path.*, **24**, 1–49 (1948)
119. KARNOFSKY, D. A., GRAEF, I., AND SMITH, H. W., *Am. J. Path.*, **24**, 275–91 (1948)
120. CRAVER, L. F., *Bull. N. Y. Acad. Med.*, **24**, 3–25 (1948)
121. PETERSON, E., THOMAS, I. A., HADDOW, A., WATKINSON, J. M., *Lancet*, **I**, 677–82 (1946)
122. WEIR, D. R., AND HEINLE, R. W., *Proc. Soc. Exptl. Biol. Med.*, **66**, 268–70 (1947)
123. LAW, L. W., *Proc. Soc. Exptl. Biol. Med.*, **66**, 158–61 (1947)
124. LAW, L. W., *Proc. Natl. Acad. Sci. U. S.*, **33**, 204–10 (1947)
125. ENGSTROM, R. M., KIRSCHBAUM, A., AND MIXER, H. W., *Science*, **105**, 255–56 (1947)
126. MURPHY, J. B., AND STURM, E., *Cancer Research*, **7**, 417–20 (1947)
127. BERMAN, L., AND AXELROD, A. R., *Am. J. Clin. Path.*, **18**, 104–29 (1948)
128. DURY, A., AND ROBIN, E. D., *Endocrinology*, **42**, 320–26 (1948)
129. BURMESTER, B. R., *Cancer Research*, **7**, 459–67 (1947)
130. FREMONT-SMITH, P., AND FAVOUR, C. B., *Proc. Soc. Exptl. Biol. Med.*, **67**, 502–4 (1948)
131. FAVOUR, C. B., *Proc. Soc. Exptl. Biol. Med.*, **65**, 269–72 (1947)
132. GRÉGOIRE, C., *Compt. rend. soc. biol.*, **140**, 1218–19 (1946)
133. LATTA, J. S., AND NELSON, W. W., *Am. J. Anat.*, **82**, 321–51 (1948)
134. HARKINS, H. N., AND LONG, C. N. H., *Am. J. Physiol.*, **144**, 661–68 (1945)
135. ELMADJIAN, F., AND PINCUS, G., *Endocrinology*, **37**, 47–49 (1945)
136. DOUGHERTY, T. F., AND WHITE, A., *Science*, **98**, 367–69 (1943)
137. DOUGHERTY, T. F., AND WHITE, A., *Endocrinology*, **35**, 1–14 (1944)
138. REINHARDT, W. O., AND LI, C. H., *Science*, **101**, 360–61 (1945)
139. REINHARDT, W. O., ARON, H., AND LI, C. H., *Proc. Soc. Exptl. Biol. Med.*, **57**, 19–21 (1944)
140. YOFFEY, J. M., REISS, M., AND BAXTER, J. S., *Nature*, **157**, 368 (1946)
141. PINCUS, G., *Recent Progress in Hormone Research*, **1**, 123–45 (Academic Press, New York, N. Y., 1947)
142. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G., AND HILLS, A. G., *J. Clin. Endocrinology*, **8**, 15–66 (1948)
143. HILLS, A. G., FORSHAM, P. H., AND FINCH, C. A., *Blood*, **3**, 755–69 (1948)
144. HELLMAN, L., WESTON, R. E., ESCHER, D. J. W., AND LEITER, L., *Federation Proc.*, **7**, 52 (1948)
145. DARROW, D. C. (Personal communication, 1947)
146. ADAMS, E. (Personal communication, 1948)
147. VALENTINE, W. N., CRADDOCK, C. G., JR., AND LAWRENCE, J. S., *Blood*, **3**, 729–55 (1948)

148. KELLEY, V. C., AND ADAMS, J. M., *J. Pediat.*, **32**, 282–87 (1948)
149. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARAMELLI, L. C., LI, C. H., AND EVANS, H. M., *J. Clin. Endocrinology*, **8**, 1–14 (1948)
150. MALMÉJAC, J., CHARDON, G., AND GROSS, A., *Bull. acad. méd. (Paris)*, **130**, 492–93 (1946)
151. LONG, C. N. H., AND FRY, E. G., *Proc. Soc. Exptl. Biol. Med.*, **59**, 67–68 (1945)
152. HECHTER, O., *Endocrinology*, **42**, 285–307 (1948)
153. STONE, D., AND HECHTER, O., *Endocrinology*, **42**, 307–15 (1948)
154. LAWRENCE, J. S., VALENTINE, W. N., AND DOWDY, A. H., *Blood*, **3**, 593–612 (1948)
155. JACOBSON, L. O., AND MARKS, E. K., *Radiology*, **49**, 286–96 (1947)
156. ELMADJIAN, F., FREEMAN, H., AND PINCUS, G., *Endocrinology*, **39**, 293–99 (1946)
157. MIKKELSEN, W. P., AND HUTCHENS, T. T., *Endocrinology*, **42**, 394–98 (1948)
158. HARRIS, S., AND HENLE, W., *J. Immunol.*, **59**, 9–20 (1948)
159. DANIELOPOLU, D., NICOLAU, C., NESTORESCO, B., GAVRILESCO, E. AND BRUCKNER, I., *Rev. immunol.*, **11**, 189–94 (1947)
160. ANDREASEN, E., AND GOTTLIEB, O., *Acta Physiol. Scand.*, **13**, 35–44 (1947)
161. EHRICH, W. E., *Ann. N. Y. Acad. Sci.*, **46**, 823–57 (1946)
162. WHITE, A., AND DOUGHERTY, T. F., *Endocrinology*, **36**, 207–17 (1945)
163. LI, C. H., AND REINHARDT, W. O., *J. Biol. Chem.*, **167**, 487–93 (1947)
164. MILNE, J., AND WHITE, A. (Unpublished data)
165. CANNON, P. R., CHASE, W. E., AND WISSLER, R. W., *J. Immunol.*, **47**, 133–47 (1943)
166. CHANUTIN, A., AND GJESSING, E. C., *J. Biol. Chem.*, **165**, 421–26 (1946)
167. GJESSING, E. C., LUDEWIG, S., AND CHANUTIN, A., *J. Biol. Chem.*, **170**, 551–69 (1947)
168. AROCHA, H. G., AND DE VENANZI, F., *Proc. Intern. Physiol. Congr., 17th Congr.*, 129 (1947)
169. BENHAMOU, E., AND GILLE, R., *Compt. rend. soc. biol.*, **141**, 792–94 (1947)
170. MONDOLFO, H., AND DE LERNER, S. J., *Farmalecta (Buenos Aires)*, **2**, 171–76 (1947)
171. CHASE, J. H., WHITE, A., AND DOUGHERTY, T. F., *J. Immunol.*, **52**, 101–12 (1946)
172. EISEN, H. N., MAYER, M. M., MOORE, D. H., TARR, R. R., AND STOERK, H. C., *Proc. Soc. Exptl. Biol. Med.*, **65**, 301–6 (1947)
173. FRIEDEN, J., AND WHITE, A. (Unpublished data)
174. STOERK, H. C., JOHN, H. M., AND EISEN, H. N., *Proc. Soc. Exptl. Biol. Med.*, **66**, 25–28 (1947)
175. DOUGHERTY, T. F., CHASE, J. H., AND WHITE, A., *Proc. Soc. Exptl. Biol. Med.*, **58**, 135–40 (1945)
176. MURPHY, J. B., AND STURM, E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 303–7 (1947)
177. PHILIPS, F. S., HOPKINS, F. H., AND FREEMAN, M. L. H., *J. Immunol.*, **55**, 289–96 (1947)
178. SPURR, C. L., *Proc. Soc. Exptl. Biol. Med.*, **64**, 259–61 (1947)
179. DOUGHERTY, T. F., CHASE, J. H., AND WHITE, A., *Proc. Soc. Exptl. Biol. Med.*, **57**, 295–98 (1944)

180. HARRIS, T. N., GRIMM, E., MERTENS, E., AND EHRICH, W. E., *J. Exptl. Med.*, **81**, 73–83 (1945)
181. MONDOLFO, H., AND HOUNIE, E., *Dia médico*, **19**, 1112–17 (1947)
182. BLOOM, W., *Handbook of Hematology*, **2**, Sect. 20, 1471–1585 (Paul B. Hoeber, Inc., New York, N. Y., 1938)
183. HARRIS, T. N., AND EHRICH, W. E., *J. Exptl. Med.*, **84**, 157–65 (1946)
184. HARRIS, T. N., RHOADS, J., AND STOKES, J., JR., *J. Immunol.*, **58**, 27–32 (1948)
185. FAGRAEUS, A., *J. Immunol.*, **58**, 1–13 (1948)
186. ROBERTS, S., ADAMS, E., AND WHITE, A., *J. Biol. Chem.*, **174**, 379–80 (1948)
187. EHRICH, W. E., AND HARRIS, T. N., *Science*, **101**, 28–31 (1945)
188. STOERK, H. C., AND EISEN, H. N., *Proc. Soc. Exptl. Biol. Med.*, **62**, 88–89 (1946)
189. STOERK, H. C., EISEN, H. N., AND JOHN, H. M., *J. Exptl. Med.*, **85**, 365–71 (1947)
190. AXELROD, A. E., CARTER, B. B., MCCOY, R. H., AND GEISINGER, R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 137–40 (1947)
191. CARTER, B. B., AND AXELROD, A. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 416–17 (1948)
192. METCHNIKOFF, E., *Immunity in Infective Diseases*, 591 pp. (Cambridge University Press, London, 1905)
193. SABIN, F. R., *J. Exptl. Med.*, **70**, 67–83 (1939)
194. EHRICH, W. E., HARRIS, T. N., AND MERTENS, E., *J. Exptl. Med.*, **83**, 373–81 (1946)
195. FAGRAEUS, A., *Acta Med. Scand.*, **130**, Suppl. No. 204, 122 pp. (1948)
196. BING, J., AND CHRISTENSEN, N. O., *Acta Med. Scand.*, **116**, 382–95 (1944)
197. BJØRNEBOE, M., AND GORMSEN, H., *Acta Path. Microbiol. Scand.*, **20**, 649 (1943)
198. BJØRNEBOE, M., GORMSEN, H., AND LUNDQUIST, F., *J. Immunol.*, **55**, 121–29 (1947)
199. GRÉGOIRE, C., *Arch. biol.* (*Liége*), **56**, 325–50 (1945)
200. LIBBY, R. L., AND MADISON, C. R., *J. Immunol.*, **55**, 15–26 (1947)
201. ROBERTS, S., ADAMS, E., AND WHITE, A. (Unpublished data)

HEART[1,2]

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Morphology

Normal.—Interest centers mainly upon conducting system and cardiac nerve supply. Walls (1), who previously dissected the atrioventricular bundle in human hearts (cf. publications in '42, '43, and '45), has recognized the atrioventricular bundle in a human embryo 8 mm. crown-rump length; he finds it arises from the atrioventricular node by a process of rapid growth. The atrioventricular node represents a part of the original atrioventricular canal which undergoes early structural specialization. Purkinje fibers were recognized at the 105 mm. stage; there is no evidence that these are fibers which have remained in an embryonic condition. The sinoatrial node was identified at 10 mm. but only at birth did it have adult cytological form. The close relationship of developing nerve elements to developing nodes is described. "This system, closely connected to the nervous system, ensures for mammals and birds a degree of circulatory efficiency not enjoyed by lower animals." Kaylor & Robb have reconstructed the specialized tissue of four human embryos (2). Walls (1) and Robb & Kaylor (3) are in general agreement with the classic work of Davies & Francis. Glomset & Birge [(4), p. 139] state: "No structure analogous to the Purkinje bundle and networks exists in man, dog or monkey." Nevertheless, some structure is present for they continue: "The bundle which has been extensively studied as the His bundle in man and dog is an insignificant muscle fasciculus." This they have named the "Ridge Fasciculus"; the course described is not unlike that of the His bundle. Their conclusions are based on: (*a*) nondistinctive cytology [but see especially Truex

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& Copenhaver (5)]; (*b*) nondistinctive staining reaction (most other investigators have found that this tissue stains unlike heart muscle); and (*c*) inference as to nonfunction because of the small cross sectional area and considerable admixture of nerves. In this regard see Robb & Turman [(6), p. 191]. Mahaim (7) has described a branch (presumably of conducting tissue) which unites the origin of the left branch to the upper part of the interventricular septum. Kaylor & Robb (3, 6) find extensive connections from the atrioventricular node, main bundle, and branches to both sides of the upper septum. Purely muscular atrioventricular connections [previously described in adult hearts by Wood *et al.* ('43) and by Öhnell ('44)] were demonstrated in human embryo serial sections by Robb, Kaylor & Turman (358). "Kent's" fibers are also reported by Mahaim (8, 9) and by Mattioli (10), however, it is not clear that these writers consider "Kent's" fibers to be ordinary cardiac muscle. Mahaim seems to use the term to signify bands of specialized tissue apart from the main bundle. Kaylor & Robb find several specialized tissue connections to the atria and septa but also find bridges of ordinary heart muscle more laterally on the atrioventricular curves. It is these ordinary muscle fibers which they designate as "Kent's." Conduction over such accessory pathways is supposed to be present in the Wolff-Parkinson-White syndrome.

Franklin (11) correlates the height of the eustachian valve with direction of (right) anterior caval blood flow; Wright *et al.* (12) investigated the vestigial valves and interatrial septum of the adult human heart; Keen (13) presents the conflicting theories concerning fetal atrial circulation and supports Sabatier's view that there are two separate streams of flow in the fetal right atrium, a phenomenon which may have practical importance in dynamic studies where the foramen ovale is patent. Piedelievre & Desdaux (14) describe cardiac and pulmonary transformations in the fetus and new born. Grossman *et al.* (15) describe the location and shape of the right atrium locating the "mid-point" as seven tenths of the total anteroposterior distance from sternum to back. These studies (11 to 15) contribute to the technique and interpretation of pressure measurements within the atrium.

Truex & Copenhaver [(5), p. 195] observed nerves, without special endings, along Purkinje tissue and some with "small club-shaped terminals" on the surface of heart muscle fibers. Presumably these were sympathetic since, with a silver stain, they are said to

be pale. Glomset & Birge (4) stress the presence of ventricular nerve trunks. Roberts (16) mentions that nerves were observed. Pannier (17) describes the sympathetic supply of the heart; he is in general agreement with Nonidez.

Of interest to embryologists are reports of two new human embryos: Robertson *et al.* (18) one of seventeen days gestation, and Watkins (19) one of 18 mm. in which he describes the coronary circulation.

Pathological (including remedial surgery).—A new syndrome compatible with some years of life has been named the "Taussig Heart" (20). The lesion involves transposition of the aorta, which arises from the right ventricle, and a large overriding pulmonary artery which receives blood from both ventricles above a septal defect. It differs from Eisenmenger's complex in three ways: (*a*) oxygen saturation of the arterial blood is abnormally low and falls still lower with exercise; (*b*) during exercise oxygen consumption per liter of ventilation decreases; and (*c*) catheterization aids diagnosis only if the catheter enters the pulmonary artery in which case the oxygen saturation will exceed that of the femoral artery. Enlargement of the heart is minimal. There is cyanosis from birth which is not the case with Eisenmenger's syndrome.

Cossio & Perianes (21) report an instrument devised to slip through the jugular vein into the right heart whereby the tricuspid valve can be cut away. This procedure prolongs life and renders more comfortable those patients suffering from "Cardiac Lung" who do not respond to medical treatment. Cohn (22) has a method for repair of interatrial septal defects in dogs; Roberts (16) reports a method of anastomosing the coronary sinus to a branch of the aorta in order to improve coronary circulation. In dogs, following Roberts' procedure, coronary ligation was not followed by infarction or death. Weinstein (23) used muscle grafts to improve vascularity. Hellerstein *et al.* (24) have removed the atrial appendages in surviving dogs. Potts (25) has devised a nonslip clamp to facilitate vascular operations.

Ashworth (26) finds heart valves relatively noncellular and nonvascular and believes these facts plus constant vibration predispose to valvular lesions. Barroso-Moguel (27) finds precollagen fibers increase in number and in argyrophilia and penetrate into rheumatic and allergic lesions. Smirnova-Zamkova (28) emphasizes the significance of basic argyrophillic substances in the pathogene-

sis of hypertension. Mukherjee has investigated the pathogenesis of coronary sclerosis (29). Experimental vascular disease caused by cholesterol is presented by Hueper (30). Faber thinks hypercholesterolemia accelerates but that a tissue factor is essential for deposition of cholesterol (31). Harper (32) and Williams (33) followed the deposit of vital dyes. Strophanthin and prostigmine produced focal necrotic areas within which the dye was deposited. Heimburger (34) produced pericarditis to study its effect on infarction in rats. Selzer & Gerbode (35) have produced experimental hypertrophy, Soslow (36) experimental heart disease, and Dick & Schwartz (37) experimental endocarditis. Bauer (38) investigated an anti-immune serum reaction; Russell (39), a possible toxin producing renal and myocardial lesions in Friedrick's ataxia.

Within the sinoatrial node of patients who had had arrhythmias, Somolinos D'Ardois (40) found sclerotic changes. Even very severe degrees of cardiac muscle damage, exclusive of the node, were never associated with rhythm change. Mahaim (41) was unable to discover any specialized tissue whatever in the heart of a thirty-six-year old man with cor-triloculare-biatrium.

Heart size as indicated by roentgen ray.—Castellanos *et al.* (45), Ceballos Labat (46), Celis *et al.* (47), Chavez *et al.* (48, 49), and Dorbecker & Deschangra (50) have worked in the field of angiocardiography. When the opaque mass is injected into the right atrium, the right heart is well defined, perhaps because of less admixture with venous blood. If it is injected into the outflow tract of the right ventricle, the pulmonary vessels are first delineated and then the left heart stands out, uncomplicated by the right. Electrokymography and fluorocardiography are discussed by Boone *et al.* (51), Ellinger *et al.* (52), Henny *et al.* (53), Holman (54), Luisada *et al.* (55), and Ring *et al.* (56), who have used these methods to study pulsations of borders of both ventricles, both atria, the great vessels, and hilar movements. In some cases the waves have been timed with reference to sphygmograms or phonograms. The waves have been related to systolic and to diastolic volume changes as well as to movements due to rotation, traction, or total shift of heart position. Asynchronism of the ventricles has also been proven.

Various methods of estimating heart area or volume have been employed (57 to 67). Although any one of these will demonstrate progressive changes of the above parameters in a single heart, if the

volume of a given heart is estimated by several methods there may be very considerable disagreement.

Miscellaneous radiographic studies are those of Foxon & Walls (68) on the mode of action of the heart of the frog, Grossman (69) on the use of spot-films, Perez Simon & Aguirre (70) on "Tomography," Hubacher *et al.* (71) on phases of heart action and movements of the mitral ring, Holmgren (72) on cineroentgenology, Holzer & Polzer (73) on "Rheocardiography," and Epstein (74) on rheumatic valvular disease without cardiac enlargement.

Physiology

Intact heart.—The limit of pH shift toward acidity tolerated by the heart was found by Gertler *et al.* (75) not to depend on the agent causing the shift. At this limit, pH 6.25, there was extreme impairment of contractility associated with an increase in amplitude of R and T waves and S-T depression. Altschule & Sulzbach (76) also report electrocardiographic changes, such as are seen during cardiac ischemia, when arterial and tissue oxygen pressures are high provided the blood pH is lowered to 6.9. Terroux *et al.* (77) find the alkaline tolerance is pH 8.4 at which level blood lactate is greatly raised and skeletal muscle rigor appears. Respiratory failure occurred at pH 7.8, electrocardiographic alterations were seen, and contractility failed terminally.

Contractility.—Szepsenwol (78) continues study of electrical excitability and spontaneous activity in explants of skeletal and heart muscle of chick embryos. Myocardium with a low threshold has precocious spontaneous activity; inactive explants with a high threshold cannot be made to beat even by acetylcholine plus physostigmine. He concludes that

> acetylcholine cannot serve as an intermediary for impulse transmission at the level of the myoneural junction in chick embryos four to five days old, at the moment spontaneous neurogenic contractions occur.

Barry (79) using embryonic heart muscle, whole or in strips, finds an abrupt acceleration if the initial rate was slow, which reaches a maximum in thirty seconds, when epinephrine in concentrations of one to ten million is added. The slower the initial rate the greater the acceleration. If the initial rate is one hundred and eighty per minute or greater, epinephrine has little effect.

Harris has previously shown that during passage of direct

current cathodal and anodal stimulation in barbitalized dogs commonly produces a coupled rhythm (a normal beat followed just after the T wave by a premature beat). When morphine-barbital sodium is used, coupling is rare; the cathodal response, even with a threshold current, is an accelerating tachycardia leading to ventricular fibrillation (this occurs less often with pentobarbital). The application of three drops of epinephrine hydrochloride (1:1000) at the stigmatic electrode on the heart of the pentobarbitalized dog promptly removes the tendency to coupling and results in more regular rhythms (80). Locally applied epinephrine has no great effect on electrical thresholds. Barium chloride and to a lesser degree calcium chloride cause coupled rhythms and increase the threshold for ectopic discharges, especially at the cathode. Moderate anoxia lowers the threshold to stimulation, severe anoxia causes a rapid rise (81).

Excitability.—Self-sustained activity in isolated atrial muscle, with maintained circulation, is the subject of several papers by Rosenblueth & García Ramos (82, 83). This preparation does not beat spontaneously. Addition of acetylcholine followed by electrical stimulation results, presently, in the development of a fast self-sustained rhythm whose rate is proportional to the rate of the previous electrical stimulation if this was above 20 per sec. This activity requires the presence of acetylcholine. These discharges end suddenly, are not stopped by refractoriness of the muscle, persist in an area less than 1 sq. cm., and are probably not maintained by a circus movement. A second slower rhythm appears after injected or locally applied epinephrine or calcium chloride have been destroyed and also follows previous electrical stimulation; the critical stimulation frequency for this type is 1 per sec.; between 2 and 4 per sec. the frequency of the self-sustained impulses is determined by that of the stimuli. The immediate effect of potassium or of acetylcholine is to stop this slow activity, a delayed effect appearing after their destruction is acceleration of discharges. Electrical studies of this activity lead the authors to disagree with Bozler's suggestion that spontaneous impulses are initiated by local potentials at the site of impulse origin. Several agents favor this automatism but all appear to act by the same mechanism, previous activity being a *sine qua non*. The acetylcholine effect in producing the rapid self-sustained rhythm and in inhibiting the slow rhythm are muscarine-like and are abolished by

atropine; the development of slow rhythm following acetylcholine destruction is neither muscarine-like nor nicotine-like; it is not prevented by atropine or by curare.

Rhythmicity.—Other studies by the same authors (84, 85, 86) have proven that an injured area of sufficient size, within the muscle bands surrounding the vena-caval orifices, if surrounded by normally conducting tissue, provides the necessary mechanism for establishment of permanent atrial flutter. A circus movement through this band of muscle was proven electrocardiographically and is also supported by the clinical electrocardiographic studies of Cabrera & Sodi Pallares (87). The reviewer remarks that these experiments seem to provide an example of limitation of excitation pathway to a single muscle band regardless of syncytial connections. Surtshin & Horlick (88) have determined the amount of acetylcholine necessary to produce second degree heart block in a given dog and then have injected ten or twenty times this amount to produce fibrillation, which occurs more readily during anemia. Schlichter (89) finds vagal stimulation and anoxia, which must act simultaneously, are main factors in the onset and perpetuation of fibrillation. Moderate anoxia reduces and extreme anoxia raises the threshold for fibrillation [see also Harris (81)]. Anoxia may be induced in intact hearts by vascular disease, by decrease in oxygen carriers (anemia), or by interference with tissue respiration.

The Gaskell effect is the production of positive variation in polarization when the vagus is stimulated. Segers (90) reports that no positive variation follows the use of acetylcholine in the resting heart and concludes the effect is "not a modification of a demarcation current but is a modification of the evanescent state of polarization represented by the after potentials." Acetylcholine and epinephrine have opposite effects. The Gaskell effect is thought to explain the inhibitory action of the vagus, but not completely because cardiomoderator vagal effects may occur without variation of polarization. Late negativity of the heart is accompanied by postsystolic contracture. In the presence of acetylcholine this contracture disappears at the same time as the late negativity. Acetylcholine does not produce tonus change in the resting heart. After potentials demonstrate the existence of a state of supernormality produced by previous activity and suppressed by acetylcholine. He concludes the Gaskell effect corresponds to suppression of excitation and not to true inhibition.

The heart of a thirteen weeks' human embryo beat several hours at room temperature in well-oxygenated Ringer's solution [Garrey & Townsend (91)]. Acetylcholine, even in high concentrations, had no inhibiting effect on the ventricles; there was some inhibiting effect on the sinus-atrium but this was not profound. "Full vagal effect is thought to develop after this time." (Reviewer has a six weeks' human embryo stained with silver showing abundant vagal supply, however, "full function" is not necessarily simultaneous with anatomical appearance.) The isolated sinus beat at all temperatures from 10° to 40°C.; at 37°C., the intrinsic rate was 157. The idioventricular rate generally averaged 1 per 3.5 of the total rate. "These rates approximate those of adult hearts when free of nervous regulation and indicate that rhythmicity pattern of the heart is established early in life."

Rijlant (92, 93) has recorded simultaneously by means of cathode oscillographs the "intrinsic" variations of potential upon the hearts of cats and land turtles (at 30°C. during ventricular fibrillation induced by electrical stimulation). Circular movements in the intact heart were not found. In turtles with an injured area in the ventricle circular movement was readily demonstrated. The number of leads (twenty to sixty) was not sufficient to exclude the possibility of circular movement in the intact heart so a device to register 216 leads simultaneously is being constructed. The present studies imply that "the activity so observed is determined locally; this corresponds to a local transitory automatism or to a pseudo automatism maintained by the delayed negativity of the preceding activation."Note that both Rosenblueth and Rijlant find an area of injury essential for the establishment of circus movement.

Refractory period.—Javier de Elío (94) briefly reviews work differentiating the absolute from the effective refractory period. Substances which prolong the effective refractory period of cardiac muscle antagonize acetylcholine. This effect is enhanced by physostigmine and prostigmine and is abolished by atropine. Action of epinephrine on the refractory period is similar in direction to that of acetylcholine but, as the dose of epinephrine is increased, there is little increase in effect, whereas with acetylcholine there is a linear relationship if log dose is plotted against the increase in maximum rate at which the atria can be driven. He suggests that impulse transmission is effected by a mechanism in which acetylcholine is the key substance and the rate of transmission is gov-

erned by the rate of formation of acetylcholine. Ramsey *et al.* (95) have a method of experimentation and of data presentation which differentiates the "absolutely" from "relatively" refractory phase. Generally physostigmine prolonged the relatively refractory period in no experiment did it shorten this period. It did not significantly affect either the absolutely refractory period or the initial threshold of turtle ventricle strips.

Conductivity.—Harris & Matlock (81) find latency to stimulus response, as well as conduction time, decrease about 10 per cent in moderate anoxia, but in severe anoxia these are lengthened from 75 to 100 per cent. Reduction of the oxygen content of inspired air to less than 8 per cent is dangerous, for there is no good sign to tell when the effects become irreversible. Segers (96, 97, 98) found a continued sequence between atrium and ventricle during complete atrioventricular block and concludes that relationships in the accessory paths are less stable than those in the His bundle, e.g., exercise could destroy the synchronization. Junctional delay in the heart of the turtle, which lacks an atrioventricular bundle, has been analyzed in detail by Gilson (99), who finds that "any path which first results in ventricular excitation renders other paths redundant." A supernormal phase of conduction recovery in the human heart is expounded by Mack, Langendorf & Katz (100).

Wiener & Rosenblueth (101) have undertaken mathematical formulation of the problem of conduction, specifically in cardiac muscle. Selfridge (102) offers mathmatical treatment of "Laws of Wave Fronts" relative to a theory of flutter. Conduction over accessory pathways is the explanation most favored for certain syndromes, particularly of the Wolff-Parkinson-White syndrome.

Cardiodynamics. (*a*) *Fractional circulation times.*—Direct measurements of cardiac output, while most valuable, are too complicated for general use, hence other methods of evaluating the circulation have evolved, among which are estimations of circulation time from some one part of the circuit to another part. End points may be objective, e.g., oximeter methods, or subjective, as when the subject reports a taste, etc. Times are longer when the patient's (or even the observer's) "reaction time" is included in the measurement, and this increase will vary from patient to patient. Nylin (351) recommends the use of decholin and has checked it against labelled phosphorus with good agreement. Normally a bitter taste appears in from 12 to 17 sec., reaches a maximum in 20

sec. and falls to a minimum in 34 sec. Increased residual blood in hypertrophied or dilated hearts dilutes the test substance and prolongs mixing so that appearance is delayed up to 42 sec. and duration is prolonged to 7 min. Wexler & Whittenberger (103) have developed a new method for measuring pulmonary to ear capillary circulation time, based on the observation that a single deep breath of 100 per cent nitrogen causes a decrease in arterial oxygen saturation which can be recorded by an oximeter. The range in thirty-five normals is found to be 4.1 to 7.0 sec., with an average of 5.2 sec. Comroe & Walker (104), using an improved method find an arterial oxygen saturation of 97.5 per cent, corresponding to their oximeter value of 96.2 per cent. Gross (352), using amyl nitrite, reports a lung to face average time of 19.5 sec. in one hundred normal subjects. Circulation time increases with increasing age, is prolonged to from 31 to 54 sec. during cardiac decompensation, but in compensated cardiac disease is only 17 to 27 sec. Amyl nitrite circulation time is considered an indirect measurement of left ventricular functional capacity. Even allowing for differences of method and agent, the disproportion between amyl nitrite time and that measured by the oximeter seems unduly great. Winsor *et al.* (105) report the use of fluorescent tracer substances in order to localize changes in circulation time. The normal adult arm to arm time is 15 to 25 sec., the arm to foot time is 25 to 35 sec., and the arterial segment time is 7 to 16 sec. In isolated right ventricular failure the fractional arm to foot time is long but the arterial segment time is normal. With left heart failure the fractional arm to arm time is normal but there is prolonged arm to foot and arterial segment time. In combined right and left failure all times are long. Acetylcholine is used by Wilburne *et al.* (106); response of the sinoatrial node producing a rate change is the end point and is objective. Nathanson & Elek (107) find that 50 per cent of compensated cardiacs have a circulation time greater than 20 sec. and also find a rough correlation between the size of the heart and prolongation of circulation time, which they ascribe to improper mixing and dilution in the increased residual blood of the dilated heart. Meneely & Chesnut (108) also find a highly significant correlation between heart volume and arm to tongue time in forty-one patients. Gernandt & Nylin (109) find, in compensated and decompensated heart disease, a valid correlation between heart volume and circulation time. Ruskin &

Rockwell (353) show that smaller doses or an increased volume containing the same dose prolonged the time. Beyond a certain optimum for each substance, increasing dose has no effect. Hamilton & Remington (110) have studied the effect of change of rate of injection. Nylin & Levander (111) report an abnormally slow circulation time in orthostatic hypotension without change in heart rate or in the electrocardiogram. The fundamental difficulty appears to be the absence of reflex regulation of the blood pressure and pulse rate.

Cardiodynamics. (*b*) *Methods of measuring output.*—The Fick measurement of cardiac output is still used as a comparative standard but recent work using right atrial blood has shown that determinations based on arm venous blood may be particularly misleading (i.e., yield low values). This results from failure to include blood returning from the head, viscera, and coronary areas in which blood the oxygen content may be very different from that of the arm. In addition, data for the three factors used in the calculation cannot be obtained simultaneously. Normal standards are: (*a*) oxygen in arterial blood, brachial, or femoral, 19 to 21 volumes per cent and (*b*) oxygen in mixed venous blood (arms, right atrium, right ventricle, pulmonary artery) 12 to 16 volumes per cent, but for the coronary sinus it is only 4 to 6 volumes per cent. Cardiac output represents the total oxygen intake divided by the arteriovenous difference. The Fick normal value is 3.1 l. per sq. m. of body surface per min., or 5.4 l. for the average sized person [Richards (112)]. Stead *et al.* (113) find that the cardiac output in 82 per cent of normals is greater than 4.5 l. per min.

White (114) describes measurement of cardiac output by a continuously recording conductivity method which registers impedence changes in a flowing stream during rapid injection of sodium chloride. Compared with the Fick method the values vary from −13 to +22 per cent in the intact dog. Roos *et al.* (115) have determined the cardiac output by an oximetric method and find the cardiac index (output in liters per sq. m. of body surface per min.) is from 2.69 to 2.91 l. Hamilton *et al.* (116) have compared Fick and dye injection methods of measuring cardiac output in man and find the average of all determinations by one method nearly the same as by the other, the average scatter being 14 per cent. Dow *et al.* (117) concluded that dye retention in the lungs is not the cause for the higher output measured by the dye method.

Nickerson *et al.* (118) have compared ballistocardiographic values with those of the Fick method and find plus or minus 25 per cent agreement for 87 per cent of normals. The ballistocardiographic values in patients with aortic insufficiency are much higher than the Fick values. In heart disease other than aortic insufficiency these values are again within plus or minus 25 per cent of the Fick determination. Gray *et al.* (119) report a correlation coefficient of 0.68 for the Fick method compared to an indirect method involving carbon dioxide equilibration. Foulger *et al.* (120) have introduced a method for determining output by means of an electronic sound meter which converts the complex pattern of low frequency cardiac vibrations into a simple resultant frequency, which gives as good a correlation as does the ballistocardiogram. Starr (121) has correlated the development of heart disease in ninety patients with their ballistocardiograms taken ten years previously. Four had abnormal records and of these, three have developed heart disease. "Those fated to have heart disease have abnormally small impacts before their disease becomes manifest." Krahl (122) describes vertical ballistocardiographs and has adapted a bathroom scale to serve for laboratory teaching of ballistocardiography (123).

Remington & Hamilton (124) have calculated the form of the ventricular ejection curve for man and dogs from the pressure pulse contour, the distensibility of the aorta, and the pulse wave transmission time. Remington & Hamilton (125) have compared stroke volume as determined from the pressure pulse with that found by dye injection and find agreement within 8.2 per cent. The predicted stroke volume in man calculated from the brachial pulse wave differs from Fick values by 17 per cent (126, 127, 128). Leishman (129) describes a new method for accurately measuring venous pressure in the neck.

Cardiodynamics. (*c*) *Discussion of output data.*—Landis (130) found prolonged excessive exercise increased the ouput without cardiac enlargement. In other experiments large infarcts did not cause decompensation when the dogs were at rest. When infarction and exercise were combined the venous pressure did rise and, if pressed, the heart did decompensate. Atrial fibrillation also did not raise venous pressure unless combined with exercise. Simple plethora caused a marked transient rise in venous pressure but to maintain this pressure infusion had to be given at the rate of from 1 to 4 ml. per kg. per min. (in man an infusion of 60 drops per min.

represents about 0.1 ml. per kg. per min.). Maintained infusion plus exercise caused a drop in venous pressure. These procedures prove increased blood volume per se is not responsible for raised venous pressure. Landis concluded that the plethora of chronic failure is compensatory, that competence does not improve as increased volume or pressure are provided. "Competence" of the heart muscle relative to the demand in the presence of raised venous pressure is important (but not the primary rise of venous pressure or the increase of blood volume). These results do not appear to be in agreement with Starling's law of the heart. Reiss (131) could produce prolonged rise of venous pressure in dogs only when all three of the following procedures were employed: (*a*) production of marked cardiac incompetence; (*b*) infusion-produced plethora; and (*c*) partial return of competence (epinephrine) Bakos (132) repeatedly charred the right ventricle with a soldering iron producing up to 75 per cent damage without materially altering the mean pulmonary or systemic pressure. In two such experiments he added injury to the left ventricle and produced simultaneous decline in pulmonary and systemic blood pressures. Brookhart (133) finds that the effective filling pressure of the dog heart can be measured most accurately as the difference between intracardiac and extracardiac thoracic pressures. Local elevation of intrathoracic pressure occurs in the region of the heart because of the distortion of the lung by the heart. Opdyke & Wiggers (134) find left atrial pressure higher than right in dogs with open chests. Jones & Schlapp (354) find fibrillation reduces the capacity of the cat heart for work by one third. [See also Remington & Hamilton (127).] The flow in the superior vena cava doubles almost immediately in dogs breathing 100 per cent nitrogen [Feldman *et al.* (135)]. Deyrup & Root (136) find that the subcutaneous injection of histamine in unanesthetized dogs caused a reduction of output and increased peripheral resistance. White *et al.* (137) report hypophysectomy permanently and greatly reduces cardiac output in dogs; however, with chronic denervation of the neural hypophysis the cardiac output remains normal (138). Nolasco & Kahrman (139) produced experimental evidence that "serious cardiac consequences are not apt to result from the use of posterior pituitary preparations administered to patients with normal hearts in therapeutic doses." Salt depletion in untraumatized dogs produces a form of peripheral vascular collapse closely resembling traumatic

shock, with decreased cardiac output, circulation rate, and blood pressure [Elkinton *et al.* (140)]. DiPalma & Reiss (141) find proof that in the beating heart cardiac muscle resembles skeletal muscle, in regard to the phenomenon of initial tension, and believe

> this explains the fact that the contractile force of the heart muscle increases with a rise in intraventricular tension. On the other hand, the contractile force decreases with increased venous return and the opposite occurs with decreased venous return.

These statements are said not to contradict the original conception of Starling's law as related to energy production, although they do seem contradictory as the law is commonly stated. The heart during systole follows the laws of an elastic sphere in which contractile stress increases as radius decreases, hence the force of contraction depends merely on its initial length (diastolic size).

Sosman (142) lists three indications for intracardiac catheterization in man: (*a*) study of hemodynamics; (*b*) accurate diagnosis in congenital heart disease; and (*c*) study of cerebral, renal, and hepatic physiology in health and disease. Brannon & Warren (143), Bing *et al.* (144), Burchell (145), Cournand *et al.* (146), Handelsman *et al.* (147), Howarth *et al.* (148), Johnson *et al.* (149), Limón Lasón (150), and Vandam *et al.* (151) employ catheterization for diagnosis and for determining the value of surgery in congenital heart disease. The Columbia University group (152), find the mean right atrial pressure in normal subjects varies from minus 2 to plus 2 mm. Hg relative to atmospheric pressure. The normal right ventricular systolic pressures were between 18 and 30 mm. Hg and averaged 25 mm. Hg. The difference between the systolic pressure and the pressure at the end of diastole, termed the right ventricular pulse pressure, ranged from 17 to 26.5 mm. Hg and averaged 22.5 mm. Hg. The normal gradient from the right arm to the right atrium is from 2 to 4 mm. Hg. These pressures are elevated in chronic pulmonary disease, are markedly elevated in left heart failure, and are disturbed if abnormal arteriovenous or arterio-arterial connections are present. In failure, the normal gradient between the right arm and the right atrium disappears. The normal pulmonary arterial pressure determined by catheterization is 10 to 15 mm. Hg [Hickam & Cargill (153)]. This value is unchanged by increased cardiac output but is elevated in emphysema, congestive heart failure, or advanced mitral stenosis. Bing *et al.* (154) report

nine successful catheterizations of the coronary veins in man and observe an average blood pressure in the coronary sinus of 12 mm. Hg. The oxygen difference of arterial and coronary venous blood is 11.3 to 18.7 volumes per cent, compared to a total systemic arteriovenous oxygen difference of 2.8 to 7.3 volumes per cent. Eckenhoff *et al.* (155, 156, 157) in dogs found a correspondingly high utilization by heart muscle. According to Gibbons (158),

In all phases of the syndrome of congestive heart failure, changes in the venous pressure and in the degree of congestion are concordant. Any initial discordance in the time relation of change in venous pressure to change in weight associated with edema can be explained by the state of those tissues affected by edema formation.

It is not clear to the reviewer exactly what is meant by "state of the tissue" or how it was measured. Threefoot *et al.* (159) agree that changes in weight and in venous pressure are concordant, both vary inversely with sodium and water excretion but neither routinely precedes the other. Otis *et al.* (160) have simultaneously measured relaxation pressure and peripheral venous pressure and can predict the venous pressure during various types of positive pressure breathing. For a given increase in intrapulmonary pressure at a constant lung volume, the venous pressure tends to rise by approximately the same increment. Cardiac output decreased in 42 patients having heart failure and an inverse relation of degree of failure to output is found by Suarez *et al.* (161), who also report a direct correlation between the degree of failure and arteriovenous oxygen difference. Howarth *et al.* (162) find cardiac output is increased when the right atrial output is lowered by venesection in the presence of severe low output failure. Cournand *et al.* (163, 164), during intermittent positive pressure breathing, demonstrated that mean cardiac output remains unchanged when the number of systoles with increased stroke volume associated with decreased pleural pressure compensated for the deficit occurring during the increasing pleural pressure phase. Otis *et al.* (165) observed that the cardiac output is 5 per cent less during voluntary hyperventilation. With normal breathing substitution of pure oxygen caused an 8.5 per cent decrease in cardiac output. Dripps & Comroe (166) report a decreased output in normal persons breathing 100 per cent oxygen. Warren *et al.* (167) found that tamponade caused a decrease in cardiac output and a fall in arterial pressure without arteriolar dilatation. The height to which

the venous pressure rises in acute pericardial tamponade depends on the blood volume and the degree of venoconstriction. Immediately after hemorrhage in dogs the cardiac output is reduced by 70 per cent; eighteen hours later saline infusion had increased it to 5 per cent above normal [Reynolds (168)]. After 30 to 40 per cent trauma in dogs the cardiac output is reduced to 10 to 25 per cent of control values [Root *et al.* (169)].

Stead *et al.* (170, 171, 172) decide that the ventricles play an active rather than a passive role in determining cardiac output because changes in ventricular relaxation and contraction were independent of wide variations in atrial pressure. Lowering the arterial pressure caused an abrupt rise in cardiac output, considered too rapid for humoral influence, but attributed to reflex stimulation of ventricular activity. Thus, they too conclude that changes in atrial pressure are not the primary factor increasing cardiac output. McMichael carried out an x-ray study during intravenous infusion; the output was regularly increased in proportion to the inflow pressure and was correspondingly decreased with venesection and venous cuffs. [Various phases of output studies are reported by the London group (173 to 177).] Lauson *et al.* (178, 179) agree that the net initial and net systolic pressures are related to the degree of stress of the filled ventricle and to the degree of its response to that stress.

Nylin (180) was able to make lateral and anteroposterior x-ray exposures, take blood samples, and measure oxygen consumption as subjects exercised on a bicycle ergometer. During exercise the ventricles emptied as well, possibly better than at rest, hence there was no increase in diastolic volume to account for the increased force of contraction and increased output. Immediately after work the heart shadow was smaller than before. He also finds that, within a certain range, the heart size and work performed correlate. The index, heart volume divided by stroke volume, is constant and is a measure of functional capacity. Normal volume varies from 400 to 700 cc. Mean volume per square meter is 2.21 l., mean error 0.31 l. The total volume divided by the surface area gives cubic centimeters per square meter, the upper normal limit for this value is 500 cc. Standing, eating, exercise, and emotion cause variations in output due to their effect upon ventricular emptying, even the entirely normal heart at rest has some residual blood. Nylin quotes Müller, who provides interesting x-ray and

necropsy data indicating that within four hours after death the heart has contracted to one half its previous estimated volume. It is suggested that the reserve strength of the heart is indirectly proportional to the residual blood. Heyer & Harrison (181) state that decompensation may be said to exist when the cardiac output and the circulation are inadequate to meet body needs, first upon effort, later even at rest. They think dyspnea and edema are caused by increased venous pressure, loss of gradient from great veins to the atrium, limitation of aeration space by fluid, and change in pulmonary membranes making oxygen transfer more difficult. Usually cardiac output is decreased slightly, moderately, or severely; however, failure may occur when the output is high in relation to the oxygen consumption of the body. Retention of sodium aggravates the condition. Stead (182) suggests a different sequence of events; over a long period of time, the output is inadequate for body needs, renal blood flow is preferentially decreased, sodium retention is caused by restricted renal flow (it being unnecessary to postulate tubular disease or hormonal influence), edema follows "forward failure," and dyspnea is caused by the sodium retention with subsequently increased blood volume, which leads to high pulmonary capillary pressure. Congestive failure is not an entity according to Dock (183), who describes two types of failure. In the first type the difficulty is mainly mechanical, for instance, hypertension and stenotic valve lesions. In this group, aside from weakness and dyspnea on exertion, no symptoms occur until the myocardium is very inefficient. His second type (seen in aortic regurgitation, arteriovenous fistulae, persistent ductus arteriosus, Paget's disease, hyperthyroidism, severe anemia, fevers, and beri-beri) presents symptoms when the myocardium is still relatively undamaged. Patients of type I usually respond to digitalis better than those of type II. Cardiac output is not necessarily related to this classification, although many subjects of type II continue to have a large output in failure. In the presence of overloading, and especially when acute pulmonary edema is present, venesection, multiple tourniquets, and also digitalis decrease venous return and increase the output. Such overdistention (once supposed to be a laboratory curiosity) again suggests limitation of Starling's law. Harrison (184) has overloaded dog hearts by various infusions and takes "the point at which the cardiac output fails to continue increasing

or begins to decline, despite the continued further rise in venous pressure" for the onset of failure. He concludes that either one must accept multiple types of failure due to various dynamic disturbances or "if a single hemodynamic defect exists in all types of heart failure, this is a defective response in relation to filling load." Such a conception relegates other factors to secondary, even though important, status. Richards (112) summarizes the physiological implications of output studies, stating that

> in normals under restricted circumstances, a relationship between cardiac stroke volume and diastolic filling pressure can be shown. In other physiological states (exercise, anxiety), something outside this law has an effect. The law applies in that part of congestive failure where cardiac output increases as venous pressure and heart size decrease. It applies about as well as one could expect for a physiologic principle derived from a heart lung preparation. The more the human heart is exposed to and reacts to nervous, vasomotor, and metabolic influences, the less it behaves in accordance with this law. The more the heart fails to respond to such influences and becomes simply a pressure-volume muscle preparation, as in congestive failure, the more closely it follows this law. The current usage of relating output to venous pressure may be more useful than the original concept of output related to volume.

Quotations from the original papers by Starling and his associates (Knowlton, Markwalder, Piper, Patterson) will establish that unintended additional meaning has inadvertently accrued to an expression which originally was sharply delimited. Thus:

> Starting with a blood pressure of 20 to 30 mm. Hg and keeping the venous inflow constant, the output at first increases with increased pressure until a maximum output is reached. This is maintained until the pressure becomes too great for the heart to overcome, when the output falls off rapidly. The point of highest pressure at which the maximum output was obtained seemed, in these experiments, to lie near the average blood pressure found normally in the animal, so that the heart began to fail as soon as the blood pressure rose above normal. . . . Venous pressure must be regarded as ONE of the mechanical means which are operative in enabling the heart to maintain an output corresponding to the blood it receives from the venous system. We wish to insist now that taking the coronary circulation into reckoning and given a constant venous inflow, the output of the heart, within much wider limits than have been previously imagined, is independent of the arterial pressures, of temperature, and of heart rate. . . . As the inflow and output gradually increase there is a slight rise of venous pressure with each increase. The venous pressure does not rise in a straight line but in a curve becoming more rapid as the limits of functional capacity of the heart are reached, until in some cases the heart becomes overdistended, is unable to deal with the blood filling its cavities, and the output diminishes, although the venous pressure rises to a maximum.

Having discussed the effect of venous pressure at varying heart rates, he continues:

> The maximum capacity is a fixed quantity for each heart and is dependent on its structural arrangements . . . at the end of each diastole the heart must be more distended when beating slowly than when beating more rapidly; to effect this distention a greater pressure is necessary, thus the heart will more readily obtain maximum distention with a slow rate and a smaller total inflow than at a more rapid rate of the heart so that there will be a limit to the degree to which a rise of venous pressure can be advantageous in causing an increased output of the heart. . . . It would seem to follow that the shorter the diastole, and, therefore, the more rapid the contraction of the heart, the greater will be the maximum output of the ventricles . . . high venous pressures being more effective in increasing output at a high rate than at a low rate. With short diastole venous pressure becomes important in hurrying up the process of lengthening muscle fibers which follows on the completion of systole.

This discussion may well be ended by Starling's own words:

> It is evident that there must be some limit to the process by which rise of venous pressure causes increased filling and increased output of the heart, this limit is probably reached when the venous pressure is high enough to produce maximum distention of the heart just as the next systole begins.

Coronary system.—The scope of this section will be greatly enhanced by reference to Gregg's article in *Physiological Reviews* (355). Glenny (185) has undertaken a systematic study of the main arteries in the region of the heart in birds. Gregg (186) reports that the anterior cardiac veins are mainly responsible for drainage of the right ventricular wall. On the left, the coronary sinus and its contributing veins play the dominant role. Venous anastomoses are extensive. When veins are occluded coronary inflow is only moderately reduced, collaterals accommodating the flow. If the entire venous system is ligated, hearts survive for hours responding to increased load with greater coronary flow. In chronic occlusion anastomoses are abundant and huge. It is doubtful that Thebesian vessels can serve as alternates for drainage. No experiments to date prove that the Thebesian openings are active with the heart *in situ*. Prinzmetal *et al.* (187 to 190) used radioactive red cells and glass spheres for coronary studies. Labelled cells were found in both ventricles but more on the side perfused, hence, numerous arterial anastomoses must be present. The largest beads to pass were one hundred and eighty micra in diameter. Anastomoses of several varieties were found between

coronary arteries and the ventricular cavities. Blood circulates in the occluded area. Intravenous injections of fluorescein (with cinematic recording) produced at first no color in the infarcted area; then color moved in concentrically from the periphery, invading the whole area within thirty seconds (normal time for coloring of entire heart is ten to sixteen seconds). Fluorescein completely and rapidly invaded the right ventricle even after coronary occlusion; this free collateral circulation may explain the relative infrequency of right sided infarcts. The subendocardial surface of the left ventricle is found to have the least adequate blood supply (as judged by labelled cell, bead, and fluorescein studies), and this fact is correlated with the well-known extensiveness of endocardial infarcts. Roberts (16) finds that the Thebesian vessels can function and that the direction of flow depends on the pressure gradient between the coronary arteries and ventricular cavities. Bobb *et al.* (191) show that cauterization at the edges of an acute infarct limits anastomoses and results in larger and more predictable lesions in dogs. Mozer (192) also discusses the role of anastomoses. Opdyke & Selkurt (193) do not find evidence of coronary reflexes following coronary occlusion. Dawes (194) locates reflex sites for cardiovascular responses following small doses of veratrine to the left ventricle. Veratrine injected into the perfused carotid sinuses has no circulatory (or respiratory) effects.

Eidlow & Mackenzie (195), Kaunitz (196), and Lyon *et al.* (197) describe anomalous origin of the left coronary from the pulmonary artery, and deleterious effects therefrom. Roberts & Loube (198) report nine new instances of congenital single coronary artery. Champy & Louwel (199) investigated "*le faisceau unitif cardio-coronarien*," by histologic means; Bunoan (200) and also Solans & Tweed (201) describe injection techniques; Lowenberg & Shumaker (202) studied vasa vasorum as related to vascular repair.

Eckenhoff *et al.* (203 to 206) do not agree with Katz *et al.* that cardiac output is of prime importance in determining coronary flow, which is very responsive to metabolites. There was no evidence of adrenergic or cholinergic constriction; pH had little and carbon dioxide had no dilatatory effect. A method for measuring blood flow by nitrous oxide is described. In the intact anesthetized dog, hypotension decreased cardiac work, the coronary flow remained relatively high, and efficiency was reduced in all experiments. This does not mean the heart was less able to do the work demanded; hence, cardiac efficiency is considered not a valid

criterion for capacity to work under varying conditions. Efficiency varied directly with the output and inversely with arterial blood pressure. The oxygen content of coronary sinus blood is 4 to 6 volumes per cent when that in the right ventricle is 12 to 16 volumes per cent and the arterial content is 19 to 21 volumes per cent. The normal mean oxygen consumption was 8.8 cc. per 100 gm. per min.; a highly significant correlation was present between oxygen consumption and coronary flow, coronary resistance, arterial blood pressure, and cardiac work (but not with cardiac output). Coronary flow will adjust either to meet a demand of the heart for oxygen or to the supply of oxygen available in the blood. Safeguards in anoxic circulatory collapse are listed as (*a*) decreased coronary tonus; (*b*) diversion of blood to the coronary bed; and (*c*) decreased work, possibly associated with increased efficiency consequent to fall in arterial blood pressure. When dogs which had had coronary sinus catheterization were necropsied, damage of the atrial and vascular endothelium was found.

Corday *et al.* (207) produced experimental coronary insufficiency, demonstrating the remarkable reserve power of the heart. Master & Auerbach (208) describe acute clinical coronary insufficiency. Fauteux (209) reduces mortality in experimental infarction by ligation of the great cardiac vein. Opdyke & Foreman (210) measured coronary flow during hypotension and shock and conclude that circulatory failure is not precipitated by inadequate coronary flow following restoration of aortic pressure by reinfusion. Ravin & Geever (211), using the Schlessinger injection method, demonstrated multiple occlusions, interarterial anastomoses, coronary aplasia, and various coronary anomalies. They relate the development of anastomoses to prognosis. Wégria (212) finds that, as heart rate increases, coronary blood flow and mean blood pressure may fall below control levels. When the tachycardia ends both return to the control level or higher; the greater the heart rate, the greater the increase in flow and blood pressure. Blood pressure usually precedes blood flow in return to normal. Biörck (213) and Weintraub & Bishop (214) evaluate clinical tests for coronary insufficiency.

Electrical Phenomena

Theoretical considerations.—The genesis of the normal electrocardiogram has been reviewed recently by Hill (215) and by Katz (216). Lepeschkin (217) (author of a German text of electrocardiog-

raphy) found in frog and cat hearts that the slow "extrinsic" component remained unchanged after applying suction electrodes, but the rapid "intrinsic" deflection was reversed. Monophasic curves before and after injury were different. Duration of ascent of the monophasic deformation curve decreases with diameter of the electrode and is only 0.006 sec. if microelectrodes are used. This time may correspond to activity in a single fiber. If the muscle surface reverses polarization during excitation [the muscle interior becoming positive, according to Curtis & Cole], rapid injury should cause instantaneous positive injury potential; this was not found to be the case. He agrees with Katz that partial depolarization occurs near an injury. A "U" wave present before injury was transformed into a negative after potential after injury. Bozler (218), with somewhat similar technique, found an R wave lasting 1 to 2 msec., a brief S and small T wave. The monophasic potential derived from the differential potential showed a rise to the maximum of 2 msec., or less, a brief spike, and following plateau. The R-R interval was the same for all parts of the neutral surface of the heart. Kaufman *et al.* (219) believe that the region of the heart being depolarized at any one time can be identified by instantaneous points on the QRS in three simultaneous unipolar limb leads (Vr, Vl, Vf) thus offering a method of determining spread of excitation [see also Kossman & Goldberg (220)]. Turman & Robb (221) applying posterior and anterior electrodes to the base of the septum, with simultaneously recorded direct transverse basal and standard leads for comparison, believe they have recorded depolarization of the atrioventricular bundle. Eyster & Gilson (222, 223) find an injured region is the source of electric energy which has the characteristics of an electromotive cell or battery. Pruitt & Valencia (224) found that injury involving only superficial muscle layers caused upward R-T displacement in epicardial but no change in adjacent cavity leads; however, cavity leads were altered if the anterior cardiac surface was in contact with a conducting medium. Endocardial injury caused upward RT displacement from cavity leads and from epicardial leads opposite the lesion. RT displacement was negative when the epicardial lead was exactly over the injury. In the turtle, upward RS-T displacement was recorded from epi- and endocardial aspects of transmural injury (also true at anterior apex of dog); the electrical forces responsible were attributed to boundaries between injured and

uninjured muscle at the periphery of the lesion. Maximal RS-T displacement results from application of muscle juice to ventricular surface (potassium). Limitations of the dipole theory are discussed. Puddu (225) offers numerous diagrams to explain mechanisms of RS-T shifts. Sodi Pallares *et al.* (226) obtained normal tracings when leading from two injured areas and conclude that injured zones within a conducting medium are not indifferent. The intracavity potential was not modified by ligation of the left anterior descending artery but was altered when potassium was applied to the anterior surface of the left ventricle. Robb (227) finds that enclosing the atria and ventricles in a glass cardiometer does not completely eliminate the QRS, also that when the right ventricle was filled with potassium chloride (not allowed to reach the left ventricle), the QRS remained short and axis deviation did not develop. Potassium chloride applied to the anterior surface of the exposed heart resulted in RS-T shifts in the limb leads. These observations force one to conclude the heart muscle, tissues in contact with the posterior mediastinum, and possibly blood may transmit electrical effects. Certainly the potentials recorded are not exclusively those from the "surface of the heart in contact with a volume conductor."

Szepsenwol (228) obtains an electrogram "analogous to that of the adult heart" from cardiac explants (in which rhythmicity and cross striation develop). The wave amplitude is greater when the electrodes are oriented in the muscle fiber direction. If several explants in one culture are each contracting, the quick wave found for single units, is replaced by a slow mono- or bipolar wave of low voltage. He suggests the T wave may be due to simultaneous contraction of muscle fibers of different frequencies. Olivo *et al.* (229) report a slow simple sinusoidal wave in contracting embryonic chick hearts, in the nine to eleven somite stage, when there are as yet no myofibrillae. When myofibrillae appear the electrocardiogram alters; at twelve to thirteen somites a rapid peak with duration of 0.01 to 0. 001 sec. is present. The slow wave, lasting tenths of a second, is attributed to activity of sarcoplasm, the quick wave to the myofibrillae. These results are claimed to support Botazzi's theory that QRS and T waves are electrical manifestations of two different processes. Chenoweth & Garb (230) have taken electrocardiograms of the isolated cat papillary muscle; these are not unlike those of the entire heart.

Durant *et al.* (231) find carbon dioxide and other gases injected to displace blood in the right ventricle cause reduction or loss of the initial ventricular deflection in direct leads.

Harris (232), Mispireta *et al.* (233), Rossier & Spühler (234), and Stroud & Feil (235) report on mechanisms of death and terminal electrocardiograms. Heyer *et al.* (236) and Weinberg (237) write concerning mental influence upon the electrocardiogram. Littmann (238, 239) explains "juvenile" patterns. Fetal electrocardiography is considered by Blondheim (240) and by Vara & Halminen (241). Cournand *et al.* (242) and Richards *et al.* (243) found the latent period from beginning of P to the beginning of the atrial systolic pressure wave averaged 0.11 sec. in eight adults, in a child with tachycardia it was 0.055 sec., and in a patient with pulmonary hypertension it was prolonged to 0.17 sec.

Calculations of axes, vectors, gradients, etc., need first hand evaluation, hence representative papers will be listed without comment: Ashman (244), Burges & Van Milaan (245), Hill (246), Meyer & Herr (247), Mascarenhas & Landulfo (248), Routier (249), Friedland & Sodi Pallares (250), Cabrera & Sodi Pallares (251), Sulzer & Duchosal (252), and Wolferth & Livezey (253). Einthoven's triangle is still much discussed: Groedel & Miller (254), Routier (255), Trocme (256), and Wilson *et al.* (257, 258, 259). The latter authors explain that Einthoven offered the calculation as an approximation, understanding its limitations; because errors are small the concept continues to be considered useful. Dolgin *et al.* (260) discovered that the potential of the Wilson terminal, while not absolutely zero, is nearer zero than any other remote contact tested. Groedel & Borchardt (261, 262) find no advantage in central terminals. Rosenblueth & García Ramos (263) have analyzed various components of the monophasic electrocardiogram of the ventricle.

The tendency to provide new terminology, especially when represented by symbols, which are not necessarily explained by the author or used in the same sense by different authors, does not make this literature more understandable to medical students, the internist, teachers, etc. (e.g. "E" may mean an Ensiform or an Esophageal lead; M and $\overline{M}$ mean what?). In regard to cavity leads one must be aware of the frequent appearance of artifacts and realize that various contours are present in different parts of a given chamber, hence a single intracavity lead can yield evidence

neither of normality or abnormality. There is no doubt that chest leads give information not to be obtained from limb leads, or that one can get more information from multiple than from single leads. Final evaluation of various methods of taking leads, or of analyzing the records once they have been taken, is not yet possible.

Biochemistry and Metabolism of the Heart

General survey.—Chen & Geiling (264) have assembled much valuable and stimulating information on the biochemistry and pharmacology of the heart; this bibliography is fairly extensive. It is believed that phosphocreatine and adenosinetriphosphate containing energy-rich phosphate bonds are capable of transforming one kind of energy to another. Normal heart muscle is reported to contain less phosphocreatine (PC) and adenosinetriphosphate (ATP) than skeletal muscle; Mangun & Myers (265) find acid-extractable purine calculated as adenine decreased in the left ventricle in myocardial insufficiency and within the right ventricle in some cases of pneumonia. Wollenberger (266), under his experimental conditions found failing hearts richer in PC than nonfailing hearts, also the failing heart had a normal supply of ATP. Both failing and nonfailing hearts contain negligible amounts of acyl phosphate. In the heart-lung preparation, nonfailing or failing, the phosphate of phosphocreatine is considerably higher than in the heart *in situ*. There is not a good correlation between amounts of phosphorylated and of total creatine in the heart of the heart-lung preparation of the dog. In the types of insufficiency studied (those induced by anesthetics, general or local, by mersalyl, or by quinacrine) failure is due to impairment of utilization and not to lack of generation of phosphate bond energy. Mommaerts & Seraidarian (267) present serious objections to the view that enzymatic dephosphorylation of ATP is the energy yielding reaction of muscular (skeletal) activity. Mommaerts (268) finds an initial drop and a slow recovery of viscosity when ATP is added to actomyosin solution in 0.5 *M* KCl. The slow recovery effect is attributed to decrease in ATP concentration through enzymatic hydrolysis; this effect is inhibited by magnesium and activated by calcium through the effect of these ions on adenosinetriphosphatase. The initial viscosity response is probably promoted but not inhibited by magnesium; the reverse is true for calcium. Other substances producing the initial effect are inosine triphosphate, inorganic

triphosphate, and inorganic pyrophosphate. The initial viscosity response is not induced by adenosinediphosphate or adenosinemonophosphate and can be obtained with enzymatically inactive myosin. It is concluded that the effect of ATP upon myosin does not depend upon its enzymatic hydrolysis. Deutsch & Lundin (269) find minute amounts of barium initiate automatic cardiac activity. This effect is specific for barium. They find ATP has no effect on cardiac muscle, while PC decreases the mechanical response by 50 per cent. Inorganic triphosphate and pyrophosphate induced considerable reversible lessening of tension. Other phosphates caused slight decrease in contraction. They consider previous conclusions that muscle response is stimulated by ATP to be due to the fact its barium salt was used. A quotation from Szent-Györgyi [(270), p. 85] is apropos:

> When trying to apply our experience gained on cross-striated muscle to other organs, the logical sequence is to start with the most closely related tissue, i.e. heart and smooth muscle. Rozsa subjected these to careful study. He prepared actin and myosin from them, and studied the properties and actions of the separate components as well as the actomyosin combination. He also tried to combine smooth-muscle myosin with cross-striated-muscle actin and vice versa. He studied the contractility and reactions with ions and ATP. His results can be summed up by saying he found no real difference between the three sorts of muscle, cross-striated, heart, and smooth muscle. The difference in the function of these three different organs is thus not a difference of this basic contractile mechanism but a difference in higher organization and regulation.

Amberson is at present not inclined to accept this sweeping claim (personal communication).

Lehninger (271) finds heart muscle suspensions possess the enzymatic equipment not only for oxidation of acetoacetate but for direct oxidation of fatty acids and suggests these oxidations proceed via the Krebs tricarboxylic cycle in heart muscle suspensions. Elliott, Kipple & Hall (272) find the output of the frog heart is improved (especially if hypodynamic) by sodium caprylate, and hence suggest that fatty acids may be used as sources of energy by frog and mammalian hearts. Sodium caprylate [Kipple, Waldman & Hall (273)] injected intravenously in cats causes arrhythmias similar to those caused by digitalis, whose action it resembles on the frog heart. In the cat a digitalis-like action is obscured by a peripheral dilating effect. This substance is useless in cardiac failure but may be helpful in the analysis of circulatory states.

Enzymes.—Potter (274) has an article of general interest on

the assay of animal tissues for respiratory enzymes. Albaum *et al.* (275) find cytochrome oxidase and succinic oxidase appear at different times in embryo chicks. Cytochrome appears earlier and at first the ratio of cytochrome oxidase to succinic oxidase is high but drops to stabilize at a constant level from the fifth day onward. Azide inhibition of the two systems is fairly constant from the third to the twenty-first day. Potter (274) concludes that a cardiac protein described by Stern which serves as a coupling link between the succinic dehydrogenase and the cytochrome-cytochrome oxidase system is not present in the embryonic chick heart before the fifth day. [Hogeboom, Claude & Hotchkiss (276) have studied distribution of cytochrome oxidase and succinic oxidase in the liver; similar studies of heart would be valuable.] Horecker & Kornberg (277) find that ferricytochrome-*c* and the cyanide ion combine in equimolar proportions to form a fairly stable cyanferricytochrome-*c* complex and discuss the physiological significance of this complex. Gobat (278) analyzed human heart and skeletal muscle for cytochrome-*c* finding individual variations in amount but always more in the myocardium; males have more than females; children have little; the amount increases in hypertrophy. One peak occurs at twenty to thirty years of age, another at fifty to sixty years, the latter is considered a presenile compensation to ward off insufficiency. Involvement of the entire body by a disease depletes cytochrome-*c* more than long duration of a localized lesion; in disease women have greater resistance to depletion than men. Proger & Delsaneas (279) have used cytochrome-*c* in patients with arteriosclerosis (intermittent claudication), which they postulate improved the utilization of oxygen in the tissues. Injected cytochrome-*c* may be inactive because it does not enter the cells.

Ames, Ziegenhagen & Elvehjem (280) discover that enzyme systems involving cytochrome-*c* are more complex than supposed; two separate types of inhibition are present whose properties resemble those attributed to copper- and iron-containg enzymes.

Méndez & Peralta (281, 282, 283) claim they have used living tissue for the first time as an index of enzymatic reaction when studying the effect of agents containing sulfhydryl groups on the Straub frog heart. Oxidizing and alkylating agents cause standstill preceded by increased contraction similar to that of cardiac glycosides. Mercaptide-forming agents produce systolic standstill preceded by a depressant effect caused by decreased excitation and

contraction of ventricular muscle. In lesser dosage these agents have a diastolic effect. These effects can be absolutely prevented by previous perfusion with a solution of the sulfhydryl "reactive" in a previously neutralized solution of glutathione ten times more concentrated than the reactive solution. Glutathione thus protects against, but does not reverse, the once established action of the above agents. Guerra & Robles (284) report inhibition of hyaluronidase by sodium salicylate in normal individuals.

Wollenberger (285) finds carbohydrate is the predominant endogenous substrate of excised guinea pig heart muscle and that the action may be increased not only by the addition of more enzymes and by increasing the catalytic power or accessibility of the enzymes, but also by making more exogenous substrate available to these enzymes. Lévy & Schwob (286) have studied the composition of Ringer's solution allowing maximum respiration of myocardial cells of the rat, guinea pig, and dog. It is known that in pancreatic or alloxan diabetes the glycogen content of the heart increases; also Lackey *et al.* have shown that myocardial glycogen storage parallels changes in blood ketone level brought about by dietary changes and that myocardial glycogen varies inversely with liver and skeletal glycogen. Recent studies (287) proved that intravenous administration of ketone bodies (pentobarbitalized rats) increased cardiac but not liver or skeletal muscle glycogen. Hegglin & Grauer (288) differentiate two forms of heart failure: (*a*) one which occurs only in general asphyxia, and presents a shortened QT, correlated with decrease of glycogen [which agrees with LePage (356)]; and (*b*) one which occurs with tissue anoxia and presents a long QT and a weak contraction but has no relation to glycogen content. According to Harris (80, 81) "the heart uses its anaerobic sources to practically complete exhaustion by the time the rapid fall in blood pressure reaches the 30 mm. Hg level," and is thereafter unable to restore its sources of chemical energy. Grauer (289) has correlated glycogenolysis with the electrocardiogram.

Gibson & Long (290) observed pyruvate oxidation in finely divided dialyzed ox heart suspensions in which inorganic phosphate, adenine nucleotide, and fumarate increase oxygen uptake and pyruvate disappearance. Pyruvate is completely oxidized to carbon dioxide and water, the molecular ratio of oxygen to

pyruvate is 2.5 and the respiratory quotient is 1.2. The presence of magnesium is necessary to prevent irreversible inactivation of the enzyme during dialysis. Sodi Pallares, Peralta & Pisanty (291) find the turtle ventricle transforms citric to pyruvic acid in small amounts. Randles *et al.* (292) report that in human vitamin B_1 deficiency the heart is unable to absorb pyruvate; many patients, especially those with neurological lesions, had T wave changes in the electrocardiogram presumably associated with outpouring of pyruvate from the heart.

Angerer & Gonzalez (293), using Fenn's technique on the hearts of two strains of rats, found Q_{O_2} values of 4.73 and 4.97 (dry weight basis). Alteration of oxygen consumption by various substrates is reported as: glucose, −8 per cent; succinate, +18 per cent; pyruvate, +34 per cent; lactate, −11 per cent. The hearts of adrenalectomized rats showed increases of Q_{O_2} values over controls of the same strain of 32 per cent and 21 per cent respectively; here the substrate alteration was: glucose, −4 per cent; succinate, +617 per cent; pyruvate, +30 per cent; lactate, +19 per cent.

Eckenhoff *et al.* (156) report the oxygen consumption of the left ventricle of the intact dog heart to be 8.8 cc. per 100 gm. per min. (S.D. ±1.1). Brown & Pearson (294) in man demonstrated a positive relationship between oxygen consumption and cardiac output. The maximum variation in output explicable by variation in oxygen consumption was 50 per cent. The amount of variation explicable by oxygen consumption might be improved beyond this 50 per cent if basal conditions and constant temperature and humidity were maintained. For each 10 per cent increase in oxygen consumption an average increase of 7.07 per cent in cardiac output results; relative changes are the same whether measured by the ballistocardiograph, right heart catheterization, or the ethyl iodide method. Wise *et al.* (295) measured oxygen consumption of a closed heart lung preparation and failed to find decrease of efficiency during failure. Butturini (296) reports an experimental cardiac study of vitamin E deficiency [see also Ensor (297)]. Shute, Shute & Vogelsang (298) present condensed clinical histories of hypertensive heart disease treated by vitamin E and discuss these results. Guest *et al.* (299) have studied a protein concentrate having a profound depressor effect on contraction (vascularin); it has

properties of an euglobulin, is heat stable, and nondialyzable. It does not lose its physiological activity when reduced with cysteine or glutathione.

Various drugs.—Krayer & Acheson (300) have reviewed the pharmacology of the veratrum alkaloids; to date the physicochemical mechanisms are less well understood than those for digitalis. Theories of action are electrical and chemical, possibly involving potassium. Saunders, Webb & Thienes (301) find that concentrations of quinidine producing typical effects in perfused hearts depress oxygen uptake of rat heart slices by 50 per cent and also reduce the ability of glucose to maintain the oxygen uptake of such slices.

Eckstein (302) mentions a cardiac factor which increases coronary flow during sympathetic stimulation. Gast & Dobson (303) observe that five different steroids (in choline-deficient rats) caused no change in heart size if normal initially, but a decrease after female hormones if initially large. Electrocardiograms showed only wide rate variation and very labile waves. Heinbecker & Rolf (304) discuss endocrine influences on cardiac output and oxygen consumption in dogs; Hoffmann *et al.* (305) describe an influence of thyroid hormone on effector systems of mammalian heart; inositol, a thyroid gland constituent, is found by Meyer (306) to decrease force of contraction and to cause arrhythmias. A cardiotropic activity of lyophilized anterior pituitary in thyroidectomized rats is reported by Hay (307). David (308) has made a clinical assay of a cardiac hormone in cardiovascular affections met in general practice. Trautman, Davis & Findley (309) find the isolated perfused mammalian heart unable to destroy renin and angiotonin. Altschule & Rosenfeld (310) find a negative nitrogen balance and increased blood lactate and pyruvate following infarction. Sodi Pallares *et al.* (311) report that L-lixose (never free in nature) is present in hearts of individuals with healthy myocardia but who died suddenly. Giarman (312) studied the toxicity of thirty antibiotic lactones on the isolated frog heart. Hall & Waldman (313) [see also Lisi (314)] find that sodium salts of caproic, heptylic, caprylic, and capric acids, used as stabilizers for human albumin solutions, tend to evoke various ectopic rhythms when given intravenously to cats in ten times the stabilizing dose. The tendency to produce abnormal rhythms increases with the length of the fatty acid chain; potassium salts abolish the rhythms

so caused. Concentrations used clinically are considered too weak to produce such automatically rhythmic ventricular foci. Winbury & Crittenden (315) find that arginine and lipine at pH 7.4 paralyze the isolated frog heart and antagonize the stimulant action of ouabain and epinephrine. Histidine has a slightly stimulant action. Intravenous injection of arginine or lipine at pH 7.4 or as the monochloride (pH 5.6 to 5.5) depresses heart rate and action. At pH 7.4 histidine base had no action: as the monohydrochloride (pH 4.0) it had the same depressant action as arginine or lipine.

The effect of various drugs upon myocardial epinephrine-sympathin concentration is reported by Raab & Humphreys (316). Von Euler (317) finds a sympathomimetic substance in mammalian heart extracts. Stansfield & Hoff (318) find tetraethylammonium bromide does not antagonize the depressant action of potassium on the frog heart.

Abdon & Borglin in 1945 reported that vagal stimulation decreased acetylcholine precursor which suggests that the latter is the source of the vagal transmitter and also found connection with cholinergic nerves unnecessary for its release. During their present studies (319), rats on choline-deficient diets developed bradycardia and then died suddenly. If choline were injected the rate quickened but the heart goes still slower when acetylcholine is added. Therefore, choline compounds are engaged in the transmission of cardiac vagal impulses. Injected choline serves as material for the synthesis of acetylcholine precursor which is essential for the liberation of free acetylcholine. The authors do not agree with Nachmansohn (329) that acetylcholine as such takes part in the propagation of impulses; they have no data which disagree with Dale's theory. The authors describe therefore two functions of the acetylcholine precursor (resynthesis and freeing of acetylcholine.) "Caffeinique" block of the turtle pneumogastric synapse was investigated by Fredericq (320). Inhibition of vagal effects by thiamine and desoxycorticosterone in the frog and rabbit is reported by Gross (321). García Ramos & Rosenblueth (322) conclude "the role of potassium is negligible, the effective transmitter of vagal impulses is acetyl choline."

A direct cardiac stimulating action of acetylcholine which appears under certain conditions is described by McDowall (323). This stimulant action involves force of contraction to a greater extent than rate. The connection of thiamine with acetylcholine

synthesis is emphasized by Minz (324). He suggests that pyruvic acid plus cocarboxylase form (*a*) acetic acid and (*b*) adenosinetriphosphate, each of which is concerned in the synthesis of acetylcholine from choline. Sadhu (325) finds acetylcholine accelerates fatigue, delays relaxation, while vitamin B_1 (thiamine) delays fatigue, but this action is absent if calcium is low. In high concentrations thiamine, even in the presence of physostigmine, annuls acetylcholine effects on the heart. Koelle (326) writes on the protection of cholinesterase against irreversible inactivation by di-isopropylfluorophosphate *in vitro*. Ether and chloroform in anesthetic concentration do not inhibit cat serum cholinesterase *in vitro* [Miquel (327)]. In higher concentrations the enzyme is inhibited *in vitro;* the ether inactivation is partly reversible. These observations support the hypothesis that parasympathetic effects observed during general anesthesia (by ether and chloroform) are not due to inhibition of cholinesterase. [See also Frommel & Piquet (328) on cholinesterase; Nachmansohn & Berman (329) on choline acetylase; Gross (330) on relationship of desoxycorticosterone to acetylcholine effects in isolated frog hearts; Hazard *et al.* (357) concerning procaine inhibition of acetylcholine in the dog; Torda *et al.* (331) on relation of acetylcholine, caffeine, and alkaloids to muscle ATP; also Torda (332) on effect of convulsants and anticonvulsants on acetylcholine metabolism.] Finally, Wright & Mendel (333) find a substance in incubated rat hearts which augments cholinesterase activity of heart muscle.

Lehman (334) prefers embryonic chick hearts for assay and gives a detailed report relating activity to constitution of cardiac glycosides. When a sugar is attached to the ring via the hydroxyl group on C_3, potency is increased nine- to thirty-seven fold; however, different sugars are not found to intensify the activity in different degrees, thus cymaroside, rhamnoside, and β-D-glucoside of strophanthidin yield identical effects when assayed by this method. If more than one sugar molecule was added the potency increased somewhat. Complete blocking of this hydroxyl group reduces activity to the approximate level of the genin. Ouabain is one-eighth as active as digitoxin; hence, the ineffective oral dose in man is not entirely a matter of nonabsorption. That the lactone ring is only part of the configuration necessary for the typical effects of cardiac glycosides is proven by study of angelica lactones, which cause primary ventricular arrest either with or without atrio-

ventricular block. The angelica group is not considered "digitalis-like" in the cat. Méndez (335) finds angelica does have digitalis-like action in the frog. When failure is produced by long activity in a heart-lung preparation, angelica fails to relieve the failure although it does in calcium-deficient hearts. Mendez, therefore, suggests that any preparation be called "digitalis-like" if it relieves failure but not otherwise. He also stresses that frog and cat methods assay cardiac glycoside toxicity but that therapeutic activity could better be assayed on the hypodynamic heart-lung preparation.

Maximal digitalization caused a decrease in potassium and calcium content of atrial muscle and a noncompensating gain in sodium [Sherrod (336)]. Ventricular muscle showed a sodium gain in the absence of any other significant change. All these shifts occurred in the absence of significant alteration in the water content of the heart. Sjoerdsma (337) reports that species variation in the output of histamine and creatine from perfused hearts of cats, rabbits, and rats exists. Digitoxin does not alter creatinine output but does decrease the histamine output in cat and rabbit hearts; the reason why tolerance to cardiac glycosides is so much greater in rats may be that their histamine output is not decreased. The implication is that digitoxin is toxic because of histamine retained in the heart. The uptake of oxygen by heart muscle is increased in the presence of glucose or lactate by various cardiac glycosides [Wollenberger (285), Lévy *et al.* (338), Finkelstein & Bodansky (339)]. Wollenberger says: "Succinate oxidation is not inhibited by ouabain, hence cytochrome-*c* is not among the diffusible catalysts whose loss is responsible for lessened oxygen uptake in presence of glucose, pyruvate, or lactate." Cardiac slices with high initial oxygen uptake in the presence of pyruvate have decreased uptake following ouabain (not preceded by stimulation). Appropriate substrate is essential for the increase of cardiac slice respiration by ouabain. The effect of ouabain is reversible. If the tissue is homogenized, ouabain does not increase the oxygen uptake. Therefore, he concludes that ouabain does not directly interfere with the catalytic function of respiratory enzymes [compare Govier's work (340) which is said to be unrelated to phenomena reported] but that the influence depends on the integrity of cellular structure; the cell surface is considered the site of action. Ouabain is thought to facilitate the entrance of

exogenous substrate into the cell and so increases respiration. The toxic depression may be due to loss of one or more diffusible respiratory catalysts. Lévy *et al.* (338) and Wollenberger (285) also report that huge doses of ouabain decrease oxygen uptake. Wollenberger (341) finds that so long as the effect of digitoxin or ouabain in the dog heart-lung preparation is inotropic, there is no change in PC or ATP. With toxic doses, at the onset of ventricular fibrillation, a 75 per cent decrease of PC occurs but no greater loss of ATP than can be accounted for by cardiac edema. Poisoned and normal hearts contain insignificant amounts of acyl phosphate. Loss of PC, reflecting turnover of labile phosphate groups of adenosinepolyphosphate (APP), has three possible explanations: (*a*) retarded synthesis of adenosinepolyphosphate resulting from the toxic depression of oxidative metabolism known to occur; (*b*) accelerated breakdown of APP; and (*c*) both retarded synthesis and accelerated breakdown. Govier (340) postulated that anoxia caused destruction of coenzyme I (i.e., ADP), which is necessary for the metabolism of lactate, a substance considered by Evans to be the preferred substrate of the heart. [Detail of this reaction is given by Soskin & Levine (342).] Govier (340) found that digitoxin added *in vitro* to an anaerobic E-deficient lactic dehydrogenase system of guinea pig heart stimulated the system. This stimulating effect did not occur in a similar system of normal heart muscle or in aerobic lactic enzyme systems, normal or E-deficient. Inhibition of coenzyme I nucleotidase (adenosinediphosphatase) by digitoxin may be the explanation. α-Tocopherol phosphate also prevents breakdown of coenzyme I. Ouabain, digitonin, cholesterol, estrone, and testosterone have effects similar to those of digitoxin, but to a lesser degree in the case of the sex hormones. Lundin (343) found that G-strophanthin had no effect on diastolic tension, increased tension during contraction, stiffness at rest or during contraction, viscosity, or the capacity for work during isometric contraction, when studied on parallel-fibered heart strips. Note that Govier reports that a cardiac glycoside operated differently under aerobic and anaerobic conditions, which leads one to consider whether the negative results of Lundin could be due to free access of oxygen, his preparations being too fresh, not hypodynamic. Sciarini, Ackerman & Salter (344) [see also White *et al.* (345, 346)] find that fresh tissue (cat papillary muscle preparation) will not respond to inotropic drugs. Using hypodynamic preparations they studied increasing

concentrations of "cardiac glycosides" first calibrating each preparation with ouabain. (Warning is given that, although the preparation must be hypodynamic, one must be certain that progressive deterioration of the tissues does not invalidate the results). Each individual papillary muscle can be assigned its own muscle constant (a). Then the fractional response, R, to the concentration of any glycoside, G, follows the equation: Log $G+\log M+\log a=0.5 \log < R(1-R) >$ where log M is the negative log-potency of the glycoside. Further study by White, Belford & Salter (345) reveals that "the over-all picture of relative potency is surprisingly similar both for the lethal dose in intact cats and for the inotropic effect on isolated papillary muscle." Maresh & Farah (347) describe a "minimal lethal dose" method of digitalis assay, find it does not give the same values as customary assay methods, advise its use for comparison to constitute a reliable basis for relative potency, and state that for each glucoside there is an optimal rate of administration. Wedd & Blair (348) find the most constant action of cardiac glycosides is to shorten the local QT interval; using this as a gauge, digitoxin, ouabain, digoxin, and Lanatoside C were qualitatively and quantitatively similar, the magnitude of the effect is proportional to the dose. Walton *et al.* (349, 350) have observed in intact hearts the action of drugs on a section of the wall of the right ventricle; the maximum effect appeared in 22 min. and was most rapid with theevetin and slowest with Tincture of Digitalis and Lanatoside C. The greatest effect on contraction appeared with theevetin and the least with Tincture of Digitalis.

This relatively new information in regard to cardiac glycosides may be summarized: Any sugar added to the ring enhances its action; these agents result in decrease of potassium, calcium, and (with toxic doses) phosphocreatine content of heart muscle. Histamine output of the heart is increased by digitalis and one author suggests that this constitutes its "toxicity." These agents increase uptake of oxygen by cardiac muscle provided some cellular structure is intact and provided there is suitable substrate for metabolism. Enzyme action probably participates, although it is shown that cytochrome-*c* is not lost and the succinate system is not inhibited. Certain effects on contraction which are "digitalis like" can be wholly prevented (but not reversed) by sulfhydryl-containing compounds. It is suggested that in toxicity some diffusible

catalyst essential to muscle respiration is lost or again that an enzyme necessary for utilization of substrate is "inhibited." It seems evident that there is biochemical (metabolic) change in failing heart muscle. There are several points in the energy cycle at which metabolic disturbance could occur and perhaps characteristic physiological changes are associated with various types of metabolic dysfunction. The primary changes in muscle are sometimes such that they can be remedied by digitalis whose direct action may be alteration of the cell permeability or perhaps action on cell proteins. Cardiac glycosides in other cases, and whenever present in toxic concentrations, may add to the metabolic breakdown; such an action is not reversible. Cardiac glycosides cannot affect the normal metabolic cycle in the same way as the abnormal cycle; this offers adequate explanation for the use of "hypodynamic" experimental preparations for the study of these drugs. The observation concerning tissue exhaustion in extreme anoxia and the fact that toxic doses of glycosides depress oxygen uptake are also pertinent. One has the feeling that after some two hundred years, almost any day, the complete mechanism of cardiac glycoside action may become known. It is not yet possible to fit anatomical, physiological, electrical, and chemical information into a complete pattern because each of these sections still has large unknown areas. An attempt to do so, although premature, will serve to indicate types of explanations which will be established at some future date.

In cardiac as in skeletal muscle, myosin exists in a semi-contracted state and metabolic energy is required to elongate the muscle. Starling's remark apropos the effect of rate on diastolic size, "To effect this distention a greater pressure is necessary" leads one to consider whether relaxation is ever a passive mechanism. Soskin & Levine quote Szent-Györgyi to the effect that "contraction is merely recoil." For some reason, not entirely understood, when the muscle is elongated it is also polarized. When it is contracted it is depolarized and cannot be restimulated until it is repolarized, presumably this is coincident with the reconversion of energy (possibly involving high-energy phosphate bonds). If reconversion is aerobic the chemical pathway is not the same as when anaerobic. The essential cause of decompensation is metabolic disturbance of heart muscle which may be due either to general or to cellular anoxia but is not necessarily due to anoxia

alone. Prolonged oxygen lack, though mild, could result in inefficient action of various enzymes so that inefficient reconversion with failure of energy production results. A similar state could be caused by lack of some essential substance (perhaps calcium or magnesium), possibly a catalyst (e.g., vitamin B_1), or by lack of suitable "substrate" derived from the blood. When such metabolic disturbances occur in muscle, changes are also occurring in polarization and depolarization potentials, and disturbances of normal physiological properties of heart muscle occur. When failure is imminent compensatory mechanisms appear which are both metabolic and mechanical. Among the latter are such sequences as have been outlined by Heyer & Harrison (181) and by Stead (182). There comes a time, as Starling realized, when increase in heart size no longer results in increased output. At this stage the myosin is stretched beyond an optimum, "recoil" no longer causes maximal shortening. When this stage is reached there is a markedly dilated heart with residual blood, and probably extreme alteration in the polarization and depolarization phenomena. Even at this stage, depending on the primary muscle disturbance, digitalis (or other cardiac glycosides) may be able to repair the metabolic breakdown of the muscle and improve its efficiency. When this does not occur, complete breakdown of cellular metabolism is followed by death. Whether the glycosides return the metabolic cycle to its original state is unknown. If gross failure has been brought about by toxins the cardiac glycosides are less able to correct the difficulty. Theoretically then, more than one type of decompensation can occur but all types at one time or another result in "defective response in relation to filling load."

LITERATURE CITED

1. WALLS, E. W., *J. Anat.*, **81**, 93–110 (1947)
2. KAYLOR, C. T., AND ROBB, J. S., *Anat. Record*, **97**, 347 (1947)
3. ROBB, J. S., AND KAYLOR, C. T., *Federation Proc.*, **6**, 189 (1947)
4. GLOMSET, D., AND BIRGE, R., *Arch. Path.*, **45**, 135–70 (1948)
5. TRUEX, R. C., AND COPENHAVER, W. M., *Am. J. Anat.*, **80**, 173–201 (1947)
6. ROBB, J. S., AND TURMAN, W. G., *Am. J. Med. Sci.*, **214**, 180–92 (1947)
7. MAHAIM, I., *Am. Heart J.*, **33**, 651–53 (1947)
8. MAHAIM, I., *Arch. inst. cardiol. Méx.*, **18**, 46–52 (1948)
9. MAHAIM, I., *Schweiz. med. Wochschr.*, **76**, 165 (1946)
10. MATTIOLI, M., *Progresso med. (Napoli)*, **3**, 177 (1947)
11. FRANKLIN, K. J., *J. Anat.*, **80**, 246–47 (1946)
12. WRIGHT, R. R., ANSON, B. J., AND CLEVELAND, H. C., *Anat. Record*, **100**, 331–55 (1948)
13. KEEN, J. A., *Clin. Proc. (Cape Town)*, **5**, 261–72 (1946)
14. PIEDELIEVRE, R., AND DESDAUX, P., *Paris Med.*, **1**, 273–80 (1946)
15. GROSSMAN, N., KONDO, B., AND KATZ, L. N., *Am. J. Physiol.*, **148**, 229–38 (1947)
16. ROBERTS, J. T., *Congr. Interam. Cardiol.*, **3**, 88 (1948)
17. PANNIER, R., *Arch. intern. pharmacodynamie*, **73**, 193–259 (1946)
18. ROBERTSON, G. G., O'NEILL, S. L., AND CHAPPELL, R. H., *Anat. Record*, **100**, 9–28 (1948)
19. WATKINS, W. M., *J. Med. Assoc. Georgia*, **36**, 231 (1747)
20. TAUSSIG, H., *Congr. Interam. Cardiol.*, **3**, 112–13 (1948)
21. COSSIO, P., AND PERIANES, I., *Congr. Interam. Cardiol.*, **3**, 17 (1948)
22. COHN, R., *Am. Heart J.*, **33** 453–57 (1947)
23. WEINSTEIN, M., AND SHAFLROFF, B. G., *Science*, **104**, 410–11 (1946)
24. HELLERSTEIN, H. K., SINAIKO, E., AND DOLGIN, M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 337 (1947)
25. POTTS, W. J., *Congr. Interam. Cardiol.*, **3**, 82 (1948)
26. ASHWORTH, C. T., *Texas State J. Med.*, **43**, 29–33 (1947)
27. BARROSO-MOGUEL, R., *Congr. Interam. Cardiol.*, **3**, 3 (1948)
28. SMIRNOVA-ZAMKOVA, A. I., *Am. Rev. Soviet Med.*, **3**, 534–38 (1946)
29. MUKHERJEE, A. B., *Calcutta Med. J.*, **44**, 33–41 (1947)
30. HUEPER, W. C., *Arch. Path.*, **41**, 130–54 (1946)
31. FABER, M., *Acta Med. Scand.*, **124**, 562–63 (1946)
32. HARPER, W. I., *J. Anat.*, **80**, 222 (1946)
33. WILLIAMS, W. L., *Anat. Record*, **97**, 99–121 (1947)
34. HEIMBURGER, R. F., *Arch. Surg.*, **52**, 677–89 (1946)
35. SELZER, A., AND GERBODE, F., *Am. J. Med.*, **4**, 623 (1948)
36. SOSLOW, M. S., *Bull. Dade County Med. Assoc. (Florida)*, **17**, 23 (1947)
37. DICK, G. F., AND SCHWARTZ, W. B., *Arch. Path.*, **42**, 159–62 (1946)
38. BAUER, F. C., JR., *Arch. Path.*, **42**, 222–27 (1946)
39. RUSSELL, D. S., *J. Path. Bact.*, **58**, 739–48 (1946)
40. SOMOLINOS D'ARDOIS, G., *Arch. Inst. cardiol. Méx.*, **17**, 570–74 (1947)
41. MAHAIM, I., *Arch. inst. cardiol. Méx.*, **18**, 42–45, (1948)
42. CARLOTTI, J., *Arch. maladies coeur et vaisseaux*, **40**, 99 (1947)
43. DAVID, P., AND PIETTE, J., *Union méd. Canada*, **77**, 149–53 (1948)

44. Hart, E. W., and Philipp, E. E., *Middlesex Hosp. J.*, **46**, 85–88 (1946)
45. Castellanos, A., Lopez, A. G., and Pereiras, R., *Arch med. infantil*, **15**, 67–77 (1946)
46. Ceballos Labat, J., *Prensa méd. mex.*, **12**, 91–93 (1947)
47. Celis, A., Gomez, C. A., and Castillo, H., *Congr. Interam. Cardiol.*, **3**, 11 (1948)
48. Chavez, I., Dorbecker, N., and Celis, A., *Am. Heart J.*, **33**, 560–93 (1947)
49. Chavez, I., Dorbecker, N., and Celis, A., *Arch. inst. cardiol. Méx.*, **17**, 121–54 (1947)
50. Dorbecker, N., and Deschangra, J., *Congr. Interam. Cardiol.*, **3**, 20 (1948)
51. Boone, B. R., Chamberlain, W. E., Gillick, F. G., Henny, G. C., and Oppenheimer, M. J., *Am. Heart J.*, **34**, 560–68 (1947)
52. Ellinger, G. F., Gillick, F. G., Boone, B. R., and Chamberlain, W. E., *Am. Heart J.*, **35**, 971–79 (1948)
53. Henny, G. C., Boone, B. R., Chamberlain, W. E., *Am. J. Roentgenol. Radium Therapy*, **57**, 409–16 (1947)
54. Holman, E., *Ann. Surg.*, **124**, 920–33 (1946)
55. Luisada, A. A., Fleischner, F. J., and Rappaport, M. B., *Am. Heart J.*, **35**, 336–66 (1948)
56. Ring, G. C., Michie, C. R., and Oppenheimer, M. J., *Federation Proc.*, **7**, 102–3 (1948)
57. Carlotti, J., Cohen, M. E., and White, P. D., *Am. Heart J.*, **34**, 552–59 (1947)
58. Cottet, P., *Radiolog. Clin.*, **16**, 103–22 (1947)
59. Denstad, J., *Nord. Med.*, **32**, 2341–47 (1946)
60. Hodges, P. C., *Radiology*, **47**, 355–59 (1946)
61. Howard, F. H., *Radiology*, **48**, 422 (1947)
62. Ludwig, H., *Helv. Med. Acta*, **13**, 352–55 (1946)
63. Marks, J. L., *Marquette Med. Rev.*, **11**, 144–50 (1946)
64. McIntosh, B. C., and Jackson, R. L., *Radiology*, **48**, 544 (1947)
65. Schwarz, G. S., *Radiology*, **47**, 360–70 (1946)
66. Segers, M., *Acta Cardiol.*, **3**, 73–77 (1948)
67. Ungerleider, H. E., *Radiology*, **48**, 129–42 (1947)
68. Foxon, G. E. H., and Walls, E. W., *J. Anat.*, **81**, 111–17 (1947)
69. Grossman, N., *Congr. Interam. Cardiol.*, **3**, 33 (1948)
70. Perez Simon, A., and Aguirre, F., *Congr. Interam. Cardiol.*, **3**, 80 (1948)
71. Hubacher, O., Liechti, A., and Nyffeler, M., *Radiolog. Clin.*, **16**, 56–72, (1947)
72. Holmgren, B. S., *Radiology*, **48**, 303 (1947)
73. Holzer, W., and Polzer, K., *Wien. med. Wochschr.*, **96**, 316 (1946)
74. Epstein, B. S., *Radiology*, **48**, 249 (1947)
75. Gertler, M. N., Hoff, H. E., and Humm, D. G., *Am. J. Physiol.*, **146**, 478 (1946)
76. Altschule, M. D., and Sulzbach, W. M., *Am. Heart J.*, **33**, 458–63 (1947)
77. Terroux, K. G., Gertler, M. N., and Hoff, H. E., *Am. J. Physiol.*, **148**, 1–13 (1947)
78. Szepsenwol, J., *Anat. Record*, **95**, 125 (1946)
79. Barry, A., *Anat. Record*, **97**, 321 (1947)

80. HARRIS, A. S., *Congr. Interam. Cardiol.*, **3**, 35 (1948)
81. HARRIS, A. S., AND MATLOCK, W. P., *Am. J. Physiol.*, **150**, 493–503 (1947)
82. GARCÍA RAMOS, J., AND ROSENBLUETH, A., *Arch. inst. cardiol. Méx.*, **17**, 302–36 (1947)
83. ROSENBLUETH, A., AND GARCÍA RAMOS, J., *Congr. Interam. Cardiol.*, **3**, 95 (1948)
84. ROSENBLUETH, A., AND GARCÍA RAMOS, J., *Arch. inst. cardiol. Méx.*, **17**, 1–19 (1947)
85. ROSENBLUETH, A., AND GARCÍA RAMOS, J., *Arch. inst. cardiol. Méx.*, **17**, 441–57 (1947)
86. ROSENBLUETH, A., AND GARCÍA RAMOS, J., *Am. Heart J.*, **33**, 677–84 (1947)
87. CABRERACOSIO, E., AND SODI PALLARES, D., *Arch. inst. cardiol. Méx.*, **17**, 850–69 (1947)
88. SURTSHIN, A., AND HORLICK, L., *Congr. Interam. Cardiol.*, **3**, 109 (1948)
89. SCHLICHTER, J. G., *Congr. Interam. Cardiol.*, **3**, 101 (1948)
90. SEGERS, M., *Arch. intern. pharmacodynamie*, **71**, 173 (1945); *Am. Heart J.*, **32**, 673 (1946)
91. GARREY, W. E., AND TOWNSEND, S. E., *Am. J. Physiol.*, **152**, 219–24 (1948)
92. RIJLANT, P., *Cardiologia*, **10**, 113–38 (1946)
93. RIJLANT, P., *Congr. Interam. Cardiol.*, **3**, 86 (1948)
94. JAVIER DE ELÍO, F., *Brit. J. Pharmacol.*, **2**, 131–42 (1947)
95. RAMSEY, R. W., FISCHER, G., AND FLINKER, M. L., *Federation Proc.*, **7**, 97, (1948)
96. SEGERS, M., LEQUIME, J., AND DENOLIN, H., *Am. Heart J.*, **33**, 685–91 (1947)
97. SEGERS, M., AND VAN HEERSWYNGHELS, J., *Acta Cardiol.*, **1**, 266–71 (1946)
98. SEGERS, M., AND VAN DOOREN, F., *Acta Cardiol.*, **1**, 99–111 (1946)
99. GILSON, A. S., JR., *Federation Proc.*, **6**, 111 (1947)
100. MACK, I., LANGENDORF, R., AND KATZ, L. N., *Am. Heart J.*, **34**, 374–89 (1947)
101. WIENER, N., AND ROSENBLUETH, A., *Arch. inst. cardiol. Méx.*, **16**, 205–15 (1946)
102. SELFRIDGE, O., *Arch. inst. cardiol. Méx.*, **18**, 177–87 (1948)
103. WEXLER, J., AND WHITTENBERGER, J. S., *J. Clin. Invest.*, **25**, 447–50 (1946)
104. COMROE, J. H., JR., AND WALKER, P., *Am. J. Physiol.*, **152**, 365–71 (1948)
105. WINSOR, T., ADOLPH, W., RALSTON, W., AND LEIBY, G. M., *Am. Heart J.*, **34**, 80–86 (1947)
106. WILBURNE, M., SCHLICHTER, J. G., GROSSMAN, M., AND CISNEROS, F., *Am. J. Physiol.*, **150**, 504–10 (1947)
107. NATHANSON, N. H., AND ELEK, S. R., *Am. Heart J.*, **33**, 464–77 (1947)
108. MENEELY, G. R., AND CHESNUT, J. L., *Am. Heart J.*, **33**, 175–81 (1947)
109. GERNANDT, B., AND NYLIN, G., *Am. Heart J.*, **32** 411–18 (1946)
110. HAMILTON, W. F., AND REMINGTON, J. W., *Am. J. Physiol.*, **148**, 25–34 (1947)
111. NYLIN, G., AND LEVANDER, M., *Ann. Internal Med.*, **28**, 723–46 (1948)
112. RICHARDS, D. W., JR., *Am. J. Med.*, **3**, 434 (1947)
113. STEAD, E. A., WARREN, J. V., AND BRANNON, S., *Am. Heart J.*, **35**, 529–41 (1948)
114. WHITE, H. L., *Am. J. Physiol.*, **151**, 45–57 (1947)
115. ROOS, A., ELAM, J. O., NEVILLE, J. F., JR., AND WHITE, H. L., *Federation Proc.*, **7**, 104 (1948)

116. Hamilton, W. G., Riley, R. L., Altyale, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, D. W., Richards, D. W., Jr., Wheeler, N. C., and Witham, A. C., *Federation Proc.*, **7**, 49 (1948)
117. Dow, P., Hahn, P. F., and Hamilton, W. F., *Am. J. Physiol.*, **147**, 493–99 (1946)
118. Nickerson, J. L., Warren, J. V., and Brannon, E. S., *J. Clin. Invest.*, **26**, 1–10 (1947)
119. Gray, F. D., Jr., Bing, R. J., and Vandam, L. D., *Am. J. Physiol.*, **151**, 245–51 (1947)
120. Foulger, J. H., Smith, P. E., and Fleming, A. J., *Am. Heart J.*, **35**, 953–61 (1948)
121. Starr, I., *Am. J. Med. Sci.*, **214**, 233 (1947)
122. Krahl, V. E., *Anat. Record*, **97**, 350 (1947)
123. Krahl, V. E., *Science*, **105**, 393–94 (1947)
124. Remington, J. W., and Hamilton, W. F., *Federation Proc.*, **6**, 121 (1947); *Am. J. Physiol.*, **144**, 536–70 (1945)
125. Hamilton, W. F., and Remington, J. W., *Am. J. Physiol.*, **148**, 14–24 (1947)
126. Remington, J. W., and Hamilton, W. F., *Am. J. Physiol.*, **148**, 25–34 (1947)
127. Hamilton, W. F., Dow, P., and Remington, J. W., *Am. J. Physiol.*, **150**, 292–98 (1947)
128. Remington, J. W., Hamilton, W. F., Noback, C. R., and Gold, J. J., *Federation Proc.*, **7**, 100 (1948)
129. Leishman, A. W. D., *Brit. Med. J.*, **II**, 773 (1946)
130. Landis, E. M., Bunn, E., Fauteux, M., and Wise, C., *J. Clin. Invest.*, **25**, 237–55 (1946)
131. Reiss, R. A., and DiPalma, J. R., *Federation Proc.*, **7**, 100 (1948)
132. Bakos, A. C. P., *Federation Proc.*, **7**, 204 (1948)
133. Brookhart, I. M., and Boyd, T. E., *Am. J. Physiol.*, **148**, 434–44 (1947)
134. Opdyke, D. F., and Wiggers, C. J., *Am. J. Physiol.*, **147**, 270–80 (1946)
135. Feldman, M., Rodbard, S., and Katz, L. N., *Congr. Interam. Cardiol.*, **3**, 22 (1948)
136. Deyrup, I. J., and Root, W. S., *Am. J. Physiol.*, **148**, 134–38 (1947)
137. White, H. L., Heinbecker, P., and Rolf, D., *Am. J. Physiol.*, **151**, 239–44 (1947)
138. White, H. L., Heinbecker, P., and Rolf, D., *Am. J. Physiol.*, **149**, 404–17 (1947)
139. Nolasco, J. B., and Kahrman, R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 108 (1947)
140. Elkinton, J. R., Danowski, T. S., and Winkler, A. W., *J. Clin. Invest.*, **25**, 120–29 (1946)
141. DiPalma, J. R., and Reiss, R. A., *Federation Proc.*, **7**, 28 (1948)
142. Sosman, M. P., *Radiology*, **48**, 441–50 (1947)
143. Brannon, E. S., and Warren, J. V., *Preventive Med.*, **1**, 13 (1946)
144. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr., *Bull. Johns Hopkins Hosp.*, **80** 107–41 (1947)
145. Burchell, H. B., *Proc. Staff Meetings Mayo Clinic*, **22**, 162–66 (1947)

146. COURNAND, A., MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D., AND BALDWIN, J., *Am. J. Physiol.*, **150**, 267–71 (1947)
147. HANDELSMAN, J. C., BING, R. J., AND VANDAM, L. D., *Federation Proc.*, **7**, 50 (1948)
148. HOWARTH, S., MCMICHAEL, J., AND SHARPEY-SCHAFER, E. P., *Brit. Heart J.*, **9**, 292–303 (1947)
149. JOHNSON, A. L., WOLLIN, D. G., AND ROSS, J. B., *Can. Med. Assoc. J.*, **56**, 249–55 (1947)
150. LIMÓN LASÓN, R., *Congr. Interam. Cardiol.*, **3**, 55 (1948)
151. VANDAM, L. D., BING, R. J., AND GRAY, F. D., JR., *Bull. Johns. Hopkins Hosp.*, **81**, 192–215 (1947)
152. BLOOMFIELD, R. A., LAUSON, H. D., COURNAND, A., BREED, E. S., AND RICHARDS, D. W., JR., *J. Clin. Invest.*, **25**, 639–64 (1946)
153. HICKAM, J. B., AND CARGILL, W. H., *Am. J. Med.*, **3**, 504 (1947)
154. BING, R. J., VANDAM, L. D., GRÉGOIRE, F., HANDELSMAN, J. C., GOODALE, W. T., AND ECKENHOFF, J. E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 239–40 (1947)
155. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., FOLTZ, E. L., AND DRIVER, R.L., *Federation Proc.*, **7**, 30 (1948)
156. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., LANDMESSER, C. M., AND HARMEL, M. H., *Federation Proc.*, **6**, 100 (1947)
157. GOODALE, W. T., LUBIN, M., ECKENHOFF, J. E., HAFKENSCHIEL, J. H., AND BANFIELD, W. G., *Am. J. Physiol.*, **152**, 341–56 (1948)
158. GIBBONS, T. B., *Am. Heart J.*, **35**, 553–66 (1948)
159. THREEFOOT, S., GIBBONS, T. B., AND BURCH, G. E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 369–72 (1947)
160. OTIS, A. B., RAHN, H., AND FENN, W. O., *Am. J. Physiol.*, **146**, 307–17 (1946)
161. SUAREZ, J. R. E., FASCIOLO, J. C., AND TAQUINI, A. C., *Am. Heart J.*, **32**, 339–56 (1946)
162. HOWARTH, S., MCMICHAEL, J., AND SHARPEY-SCHAFER, E. P., *Clin. Sci.*, **6**, 41–50 (1946)
163. COURNAND, A., MOTLEY, H. L., AND WERKO, L., *Federation Proc.*, **6**, 92 (1947)
164. COURNAND, A., AND MOTLEY, H. L., *Am. J. Physiol.*, **152**, 162–74 (1948)
165. OTIS, A. B., RAHN, H., BRONTMAN, M., MULLINS, L. J., AND FENN, W. O., *J. Clin. Invest.*, **25**, 413–21 (1946)
166. DRIPPS, R. D., AND COMROE, J. H., JR., *Am. J. Physiol.*, **149**, 277–91 (1947)
167. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR., AND MERRILL, A. J., *Am. Heart J.*, **31**, 418–25 (1946)
168. REYNOLDS, M., *Federation Proc.*, **7**, 101 (1948)
169. ROOT, W. S., WOLCOTT, W. W., AND GREGERSEN, M. I., *Am. J. Physiol.*, **151**, 34–44 (1947)
170. STEAD, E. A., JR., HICKAM, J. B., AND WARREN, J. V., *Trans. Assoc. Am. Physicians*, **60**, 74–76 (1947)
171. STEAD, E. A., JR., AND WARREN, J. V., *Arch. Internal Med.*, **80**, 237–48 (1947)
172. WARREN, J. V., AND BRANNON, E. S., *Am. J. Med.*, **4**, 193–200 (1948)
173. HOWARTH, S., MCMICHAEL, J., AND SHARPEY-SCHAFER, E. P., *Brit. Heart J.*, **8**, 255 (1946)

174. McMichael, J., *Brit. Heart J.*, **9**, 70 (1947)
175. McMichael, J., *Brit. Med. J.*, **I**, 356 (1948)
176. Howarth, S., McMichael, J., and Sharpey-Schafer, E. P., *Clin. Sci.*, **6**, 187 (1947)
177. McMichael, J., *Edinburgh Med. J.*, **55**, 65–77 (1948)
178. Lauson, H. D., Bloomfield, R. A., and Cournand, A., *Am. J. Med.*, **1**, 315–36 (1946)
179. Lauson, H. D., Cournand, A., and Bloomfield, R. A., *J. Clin. Invest.*, **25**, 913 (1946)
180. Nylin, G., *Arch. inst. cardiol. Méx.*, **17**, 243–72 (1947)
181. Heyer, H. E., and Harrison, T. R., *Modern Concepts Cardiovas. Disease*, **16** (11), (1947)
182. Stead, E. A., *Modern Concepts Cardio vas. Disease*, **16** (12), (1947)
183. Dock, W., *J. Mt. Sinai Hosp. N. Y.*, **13**, 310 (1947)
184. Harrison, T. R., *Congr. Interam. Cardiol.*, **3**, 36 (1948)
185. Glenny, I. H., *Can. J. Research* [D]**24**, 31–39 (1946)
186. Gregg, D. J., and Shipley, R. E., *Am. J. Physiol.*, **151**, 13–25 (1947)
187. Prinzmetal, M., and Simkin, B., *Am. Heart J.*, **33**, 420–42 (1947)
188. Prinzmetal, M., and Bergman, H. C., *Am. J. Med.*, **4**, 617 (1948)
189. Prinzmetal, M., and Simkin, B., *Arch. inst. cardiol. Méx.*, **18**, 122–56 (1948)
190. Prinzmetal, M., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Sinubin, B., and Sabin, S. S., *Am. Heart J.*, **35**, 689–717 (1948)
191. Bobb, J. R. R., Kunze, D. C., and McCall, W., Jr., *Federation Proc.*, **7**, 9 (1948)
192. Mozer, J. J., *Bruxelles méd.*, **27**, 696–707 (1947)
193. Opdyke, D. F., and Selkurt, E. E., *Congr. Interam. Cardiol.*, **3**, 71 (1948)
194. Dawes, G. S., *J. Pharmacol. Exptl. Therap.*, **89**, 325–42 (1947)
195. Eidlow, S., Mackenzie, E. R., *Am. Heart J.*, **32**, 243–49 (1946)
196. Kaunitz, P. E., *Am. Heart J.*, **33**, 182–205 (1947)
197. Lyon, R. A., Johansmann, R. J., and Dodd, K., *Am. J. Diseases Children*, **72**, 675–90 (1946)
198. Roberts, J. T., and Loube, S. D., *Am. Heart J.*, **34**, 180–208 (1947)
199. Champy, C., and Louwel, J., *Arch. maladies coeur et vaisseaux*, **39**, 141–54 (1946)
200. Bunoan, P. B., *Am. J. Med. Technol.*, **12**, 277–81 (1946)
201. Solans, A. H., and Tweed, P., *Am. Heart J.*, **33**, 477–89 (1947)
202. Lowenberg, R. J., and Shumacker, H. B., Jr., *Yale J. Biol. Med.*, **20**, 395–401 (1948)
203. Eckenhoff, J. E., Hafkenschiel, J. H., and Landmesser, C. M., *Am. J. Physiol.*, **148**, 582–96 (1947)
204. Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Dety, S. S., *Am. J. Physiol.*, **152**, 356–64 (1948)
205. Eckenhoff, J. E., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L., *Am. J. Physiol.*, **152**, 545–54 (1948)
206. Hafkenschiel, J. H., and Eckenhoff, J. E., *Federation Proc.*, **7**, 224 (1948)
207. Corday, E., Spitzler, R., Bergman, H. C., Kruger, H. E., and Prinzmetal, M., *Congr. Interam. Cardiol.*, **3**, 15 (1948)

208. MASTER, A. M., AND AUERBACH, O., *U. S. Naval Med. Bull.*, **47**, 226–37 (1947)
209. FAUTEUX, M., *Am. Heart J.*, **31**, 260–69 (1946)
210. OPDYKE, D. F., AND FOREMAN, R. C., *Am. J. Physiol.*, **148**, 726–39 (1947)
211. RAVIN, A., AND GEEVER, E. F., *Arch. Internal Med.*, **78**, 125–38 (1946)
212. WÉGRIA, R., AND KEATING, R. P., *Congr. Interam. Cardiol.*, **3**, 122 (1948)
213. BIÖRCK, G., *Am. Heart J.*, **32**, 689–96 (1946)
214. WEINTRAUB, H. J., AND BISHOP, L. F., *Ann. Internal Med.*, **26**, 741–63 (1947)
215. HILL, A., *Brit. Heart J.*, **8**, 147–56 (1946)
216. KATZ, L. N., *Physiol. Revs.*, **27**, 398–435 (1947)
217. LEPESCHKIN, E., *Congr. Interam. Cardiol.*, **3**, 51 (1948)
218. BOZLER, E., *Federation Proc.*, **6**, 79 (1947)
219. KAUFMAN, W., CHERNOFF, H. M., AND NAHUM, L. H., *Federation Proc.*, **7**, 316 (1948)
220. KOSSMAN, C. E., AND GOLDBERG, H. H., *Am. Heart J.*, **33**, 308–18 (1947)
221. TURMAN, W. G., AND ROBB, J. S., *Federation Proc.*, **7**, 126 (1948)
222. EYSTER, J. A. E., AND GILSON, W. E., *Am. J. Physiol.*, **150**, 572 (1947)
223. EYSTER, J. A. E., AND GILSON, W. E., *Federation Proc.*, **6**, 101 (1947)
224. PRUITT, R. P., AND VALENCIA, F., *Am. Heart J.*, **35**, 161–97 (1948)
225. PUDDU, V., *Arch. maladies coeur et vaisseaux*, **40**, 14–31 (1947)
226. SODI PALLARES, D., CABRERACOSIO, E., TORRE, J. M., SOBERÓN, J., AND PELLON, R., *Arch. inst. cardiol. Méx.*, **16**, 266–92 (1946)
227. ROBB, J. S., *Federation Proc.*, **7**, 103 (1948)
228. SZEPSENWOL, J., *Anat. Record*, **98**, 67–85 (1947)
229. OLIVO, O. M., PETRALIA, S., AND RICAMO, R., *Boll. soc. ital. biol. sper.*, **22**, 911–13 (1946)
230. CHENOWETH, M. B., AND GARB, S., *Federation Proc.*, **7**, 211 (1948)
231. DURANT, T., LONG, J., AND OPPENHEIMER, M. J., *Proc. Soc. Exptl. Biol. Med.*, **66**, 479–81 (1947)
232. HARRIS, A. S., *Am. Heart. J.*, **35**, 895–909 (1948)
233. MISPIRETA, D., GUIBOVICK, C., AND NEIRA, J., *Congr. Interam. Cardiol.*, **3**, 63 (1948)
234. ROSSIER, P. H., AND SPÜHLER, O., *Cardiologia*, **11**, 60 (1946)
235. STROUD, M. W., AND FEIL, H. S., *Am. Heart J.*, **35**, 910–23 (1948)
236. HEYER, H. E., WINANS, H. M., AND PLESSINGER, V. I., *Am. J. Med. Sci.*, **214**, 23 (1947)
237. WEINBERG, S. J., *Proc. Soc. Exptl. Biol. Med.*, **66**, 128 (1947)
238. LITTMANN, D., *Am. Heart J.*, **32**, 370–82 (1946)
239. LITTMANN, D., *Am. J. Med.*, **3**, 626 (1947)
240. BLONDHEIM, S. H., *Am. Heart J.*, **34**, 35 (1947)
241. VARA, P., AND HALMINEN, E., *Acta Obstet. Gynecol. Scand.*, **26**, 249–62 (1946)
242. COURNAND, A., AND MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D., AND RICHARDS, D. W., JR., *Proc. Soc. Exptl. Biol. Med.*, **63**, 148–51 (1946)
243. RICHARDS, D. W., Jr., AND COURNAND, A., *Trans. Assoc. Am. Physicians*, **60**, 65–73 (1947)
244. ASHMAN, R., *Arch. inst. cardiol. Méx.*, **16**, 139–53 (1946)
245. BURGES, H. C., AND VAN MILAAN, J. B., *Brit. Heart J.*, **8**, 157–61 (1946)

246. HILL, R. F., *Am. Heart J.*, **32**, 72–81 (1946)
247. MEYER, P., AND HERR, R., *Arch. maladies coeur et vaisseaux*, **39**, 203–8 (1946)
248. MASCARENHAS, A., AND LANDULFO, J., *Arch. inst. cardiol. Méx.*, **18**, 86–111 (1948)
249. ROUTIER, R., *Acta Cardiol.*, **1**, 312–26 (1946)
250. FRIEDLAND, C. K., AND SODI PALLARES, D., *Arch. inst. cardiol. Méx.*, **17**, 293–301 (1947)
251. CABRERACOSIO, E., AND SODI PALLARES, D., *Arch. inst. cardiol. Méx.*, **17**, 356–83 (1947)
252. SULZER, R., AND DUCHOSAL, P. W., *Helv. Physiol. et Pharmacol. Acta*, **4**, 285–95 (1946)
253. WOLFERTH, C. C. AND LIVEZEY, M. M., *Am. Heart J.*, **34**, 1–18 (1947)
254. GROEDEL, F. M., AND MILLER, M., *Exptl. Med. Surg.*, **5**, 19–32 (1947)
255. ROUTIER, D., *Acta Cardiol.*, **1**, 14–17 (1946)
256. TROCME, C., *Arch. maladies coeur et vaisseaux*, **39**, 80–88 (1946)
257. WILSON, F. N., BRYANT, J. M., AND JOHNSTON, F. D., *Congr. Interam. Cardiol.*, **3**, 125 (1948)
258. WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F., AND BARKER, P. S., *Am. Heart J.*, **32**, 277–310 (1946)
259. WILSON, F. N., JOHNSTON, F. D., AND KOSSMANN, C. E., *Am. Heart J.*, **33**, 594–603 (1947)
260. DOLGIN, M., GRAU, S., AND KATZ, L. N., *Congr. Interam. Cardiol.*, **3**, 19 (1948)
261. GROEDEL, F. M., AND BORCHARDT, P. R., *Exptl. Med. Surg.*, **5**, 1–18 (1947)
262. GROEDEL, F. M., *Exptl. Med., Surg.*, **5**, 75–84 (1947)
263. ROSENBLUETH, A., AND GARCÍA RAMOS, J., *Arch inst. cardiol. Méx.*, **16**, 45–57, (1946)
264. CHEN, G., AND GEILING, E. M. K., *Schweis. med. Wochschr.*, **77**, 25–28 (1947)
265. MANGUN, G. H., AND MYERS, V. C., *Arch. Internal Med.*, **78**, 441–46 (1946)
266. WOLLENBERGER, A., *Am. J. Physiol.* **150**, 733 (1947)
267. MOMMAERTS, W. F. H. M., AND SERAIDARIAN, K., *J. Gen. Physiol.*, **30**, 40 (1947)
268. MOMMAERTS, W. F. H. M., *J. Gen. Physiol.*, **31**, 361–75 (1948)
269. DEUTSCH, A., AND LUNDIN, G., *Acta Physiol. Scand.*, **11**, 373–79 (1946)
270. SZENT-GYÖRGYI, A., *Muscular Contraction*, p. 85 (Academic Press, New York City, 1947)
271. LEHNINGER, A. L., *J. Biol. Chem.*, **165**, 131–45 (1946)
272. ELLIOTT, H. W., KIPPLE, H. M., AND HALL, V. E., *J. Pharmacol. Exptl. Therap.*, **89**, 14–17 (1947)
273. KIPPLE, H. M., WALDMAN, M. S., AND HALL, V. E., *J. Pharmacol. Exptl. Therap.*, **89**, 313–19 (1947)
274. POTTER, V. R., *J. Biol. Chem.*, **165**, 311–24 (1946)
275. ALBAUM, H. G., NOVIKOFF, A. B., AND OGUR, M., *J. Biol. Chem.*, **165**, 125–30 (1946)
276. HOGEBOOM, G. H., CLAUDE, A., AND HOTCHKISS, R. D., *J. Biol. Chem.*, **165**, 615–29 (1946)
277. HORECKER, B. L., AND KORNBERG, A., *J. Biol. Chem.*, **165**, 11–20 (1946)

278. GOBAT, Y., *Helv. Med. Acta*, **14**, 45–73 (1947)
279. PROGER, S., AND DELSANEAS, D. J., *Bull. New Engl. Med. Center*, **8**, 145–49 (1946)
280. AMES, S. R., ZIEGENHAGEN, A. J., AND ELVEHJEM, C. A., *J. Biol. Chem.*, **165**, 81–89 (1946)
281. MÉNDEZ, R., *Science*, **104**, 5–6 (1946)
282. MÉNDEZ, R., AND PERALTA, B., *Arch. inst. cardiol. Méx.*, **17**, 235–42 (1947)
283. MÉNDEZ, R., AND PERALTA, B., *J. Pharmacol. Exptl. Therap.*, **90**, 128–37 (1947)
284. GUERRA, F., AND ROBLES, G. J., *Arch. inst. cardiol. Méx.*, **16**, 293–301 (1946)
285. WOLLENBERGER, A., *J. Pharmacol. Exptl. Therap.*, **91**, 39–47 (1947)
286. LÉVY, J., AND SCHWOB, A., *Bull. soc. chim. biol.*, **28**, 642–47 (1946)
287. LACKEY, R. W., BUNDE, C. A., AND HARVIES, L. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 433–36 (1947)
288. HEGGLIN, R., AND GRAUER, H., *Helv. Med. Acta*, **13**, 356–62 (1946)
289. GRAUER, H., *Praxis (Bern)*, **36**, 202 (1947)
290. GIBSON, L. H., AND LONG, C., *Biochem. J.*, **41**, 230–35 (1947)
291. SODI PALLARES, E., PERALTA, B., AND PISANTY, J., *Arch. inst. cardiol. Méx.* **17**, 516–20 (1947)
292. RANDLES, F. S., HIMWICH, W. A., HOMBURGER, A., AND HIMWICH, H. E., *Am. Heart J.*, **33**, 341–45 (1947)
293. ANGERER, C. A., AND GONZALEZ, Q. J., *Federation Proc.*, **6**, 69–70 (1947)
294. BROWN, H. R., AND PEARSON, R., *Proc. Soc. Exptl. Biol. Med.*, **65**, 307–9 (1947)
295. WISE, W., MEYER, S., KATZ, L. N., LENDRUM, B., AND JOCHIM, K., *Am. J. Physiol.*, **147**, 28–38 (1946)
296. BUTTURINI, U., *Giorn. clin. med.*, **27**, 400–10 (1947)
297. ENSOR, C. R., *Am. J. Physiol.*, **147**, 477–80 (1946)
298. SHUTE, E. V., SHUTE, W. E., AND VOGELSANG, A. B., *Med. Record*, **160**, 230 and 279 (1947)
299. GUEST, M. M., MURPHY, R. C., BODNAR, S. R., WALL, A. G., AND SEEGERS, W. H., *Am. J. Physiol.*, **150**, 471–79 (1947)
300. KRAYER, O., AND ACHESON, G. H., *Physiol. Revs.*, **26**, 383–446 (1946)
301. SAUNDERS, P. R., WEBB, J. L., AND THIENES, C. H., *Federation Proc.*, **7**, 253, 1948.
302. ECKSTEIN, R. W., STROUD, M. W., PRITCHARD, W. H., AND DOWLING, C. V. *J. Lab. Clin. Med.*, **32**, 1515–16 (1947)
303. GAST, J. H., AND DOBSON, H. L., *Federation Proc.*, **7**, 40 (1948)
304. HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **151**, 239–44 (1947)
305. HOFFMANN, F., HOFFMANN, E. J., AND TALESNIK, J., *Am. J. Physiol.*, **148**, 689–99 (1947)
306. MEYER, A. E., *Proc. Soc. Exptl. Biol. Med.*, **62**, 111–12 (1946)
307. HAY, E. C., *Am. J. Med. Sci.*, **212**, 535–37 (1946)
308. DAVID, P. L., *Union méd. Canada*, **75**, 835–36 (1946)
309. TRAUTMAN, W. J., DAVIS, W. D., AND FINDLEY, T., *J. Lab. Clin. Med.*, **32**, 1482–85 (1947)
310. ALTSCHULE, M. D., AND ROSENFELD, F. M., *Arch. Internal Med.*, **80**, 74–80 (1947)

311. Sodi Pallares, E., Velez Orozco, F., and Rivero Carvallo, J., *Arch. inst. cardiol. Méx.*, **17**, 575–81 (1947)
312. Giarman, M. J., *Federation Proc.*, **7**, 222 (1948)
313. Hall, V. E., and Waldman, M. S., *J. Pharmacol. Exptl. Therap.*, **88**, 221–31 (1946)
314. Lisi, A. G., *Federation Proc.*, **7**, 240 (1948)
315. Winbury, M., and Crittenden, P., *J. Pharmacol. Exptl. Therap.*, **90**, 293–303 (1947)
316. Raab, W., and Humphreys, R. J., *J. Pharmacol. Exptl. Therap.*, **89**, 64–76 (1947)
317. Euler, U. S. v., *J. Physiol. (London)*, **105**, 38–44 (1946)
318. Stansfield, H., and Hoff, H. E., *Federation Proc.*, **6**, 210 (1947)
319. Abdon, N. O., and Borglin, N. E., *Acta Pharmacol. Toxicol.*, **2**, 247–63 (1946)
320. Fredericq, H., *Arch. intern. physiol.*, **55**, 67–72 (1947)
321. Gross, E., *Helv. Physiol. et Pharmacol. Acta*, **4**, 47–48 (1946)
322. García Ramos, J., and Rosenblueth, A., *Arch. inst. cardiol. Méx.*, **17**, 384–405 (1947)
323. McDowall, R. J. S., *J. Physiol. (London)*, **104**, 392–403 (1946)
324. Minz, B., *Proc. Soc. Exptl. Biol. Med.*, **63**, 280–81 (1946)
325. Sadhu, D. P., *Am. J. Physiol.*, **147**, 233–36 (1946)
326. Koelle, G. B., *J. Pharmacol. Exptl. Therap.*, **88**, 232–37 (1946)
327. Miquel, O., *J. Pharmacol. Exptl. Therap.*, **88**, 190–93 (1946)
328. Frommel, E., and Piquet, J., *Arch. intern. pharmacodynamie*, **72**, 312–20 (1946)
329. Nachmansohn, D., and Berman, M., *J. Biol. Chem.*, **165**, 551–63 (1946)
330. Gross, F., *Experientia*, **2**, 191–92 (1946)
331. Torda, C., and Wolff, H. G., *Am. J. Physiol.*, **152**, 86–92 (1948)
332. Torda, C., and Wolff, H. G., *Am. J. Physiol.*, **151**, 345–54 (1947)
333. Wright, M., and Mendel, B., *J. Biol. Chem.*, **165**, 389–90 (1946)
334. Lehman, R. A., *Proc. Soc. Exptl. Biol. Med.*, **63**, 372–75 (1946)
335. Méndez, R., *Arch. inst. cardiol. Méx.*, **17**, 83–97 (1947)
336. Sherrod, T. R., *Proc. Soc. Exptl. Biol. Med.*, **65**, 89–90 (1947)
337. Sjoerdsma, A., Kun, E., Schueler, F. W., and do Valle, J. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 144–47 (1948)
338. Lévy, J., Libert, O., and Schwob, A., *Bull. soc. chim. biol.*, **29**, 269 (1947)
339. Finkelstein, M., and Bodansky, O., *Federation Proc.*, **7**, 218 (1948)
340. Govier, W. M., Yanz, N., and Grelis, M. E., *J. Pharmacol. Exptl. Therap.* **88**, 373–81 (1946)
341. Wollenberger, A., *Federation Proc.*, **7**, 266 (1948)
342. Soskin, S., and Levine, R., *Carbohydrate Metabolism*, 315 pp. (Univ. of Chicago Press, Chicago, Ill., 1946)
343. Lundin, G., *Acta Physiol. Scand.*, **11**, 221–29 (1946)
344. Sciarini, L. J., Ackerman, E. M., and Salter, W. T., *J. Pharmacol. Exptl. Therap.*, **92**, 432–43 (1948)
345. White, W. F., Belford, J., and Salter, W. T., *J. Pharmacol. Exptl. Therap.*, **92**, 443–46 (1948)

346. WHITE, W. F., AND SALTER, W. T., *J. Pharmacol. Exptl. Therap.*, **88**, 1–9 (1946)
347. MARESH, G. J., AND FARAH, A. E., *J. Pharmacol. Exptl. Therap.*, **90**, 304 (1947)
348. WEDD, A. M., AND BLAIR, H. A., *J. Pharmacol. Exptl. Therap.*, **90**, 211 (1947)
349. WALTON, R. P., AND BRODIE, O. J., *J. Pharmacol. Exptl. Therap.*, **90**, 26–41 (1947)
350. WALTON, R. P., PATTON, M. F., JONES, H. P., AND LEARY, J. S., *Federation Proc.*, **7**, 262 (1948)
351. NYLIN, G., *Am. Heart J.*, **30**, 1–11 (1945)
352. GROSS, D., *Am. Heart J.*, **30**, 19–30 (1945)
353. RUSKIN, A., AND ROCKWELL, P., *Proc. Soc. Exptl. Biol. Med.*, **60**, 40–47 (1945)
354. JONES, A. M., AND SCHLAPP, W., *J. Physiol. (London)*, **104**, 23–24 (1945)
355. GREGG, D. E., *Physiol. Revs.*, **26**, 28–46 (1946)
356. LEPAGE, G. A., *Am. J. Physiol.*, **146**, 267–81 (1946)
357. HAZARD, R., CORTEZZIANI, E., AND CHEYMOL, J., *Compt. rend. soc. biol.*, **138**, 262–64 (1944)
358. ROBB, J. S., KAYLOR, C. T., AND TURMAN, W. G., *Scientific Exhibit Program*, **254** (Am. Med. Assoc., 1947)

PERIPHERAL CIRCULATION[1]

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Blood Volume

Methods.—In 1945 Cruickshank & Whitfield (1) challenged the customary techniques for estimation of blood volume by the use of the dye T 1824 (Evans blue), claiming that mixing was complete in about one minute (cat) and that the alleged mixing phase was profoundly influenced by dye absorption mechanisms which should be blocked before any determination. Since then many experimental studies on this question have appeared. Pairs of determinations of plasma volume by two injections of T 1824 at about one-hour intervals showed no difference between the pairs, and Bonnycastle (2) concludes that the blocking of a dye absorption mechanism is of no value.

The time-concentration curve after injection of T 1824 into dogs has been reanalyzed by Miller (3) in three phases. The first phase, about five minutes, represents the mixing of the dye with the circulating blood. The second phase, about an hour, represents the passage of dye into "non-circulating plasma" vascular backwaters and out of the axial flow into the slowly moving parietal layers of the blood stream. After that is complete, there is a steady disappearance due to dye leaving the blood stream. Thus Miller sees a three-phase curve with a short mixing phase superimposed on a longer phase during which circulating plasma mixes with the "non-circulating" plasma; this in turn is superimposed on the slowest disappearance slope. He advocates extrapolating both the latter phases to zero to measure circulating plasma and total plasma, the difference being about 14 per cent. Miller (4) further showed that the liver is not significantly concerned with the excretion of T 1824 into the bile.

Lawson and associates (5 to 10) studied the mixing of red cell concentrates and of plasma injected into anesthetized dogs. The mixing time was usually less than three minutes. When plasma was injected into an animal previously dyed with T 1824, they found

[1] This review covers the period from July, 1947 to July, 1948.

that, immediately this mixing period was over, the concentration of the dye continued to fall exponentially as it had been doing before the undyed plasma was injected. However when dyed plasma was injected, the concentration of dye fell rapidly for twenty minutes or more before achieving an approximately exponential rate of disappearance. They attribute this rapid fall to dye leaving the cardiovascular system and being fixed in the tissues as suggested by LeVeen & Fishman (11). A truly exponential rate of disappearance is not found until two or more hours after injection of the dye. Lawson *et al.* recognize three phases of dye disappearance after the initial mixing is complete: (*a*) an initial rapid disappearance phase (up to one hour) in which the concentration at any time is equal to the concentration one minute after injection divided by a fractional power (about 0.055) of the elapsed time ($C_t = C_1$ min./$T^{0.055}$); (*b*) a transition phase (one to three hours); and (*c*) an exponential phase. Each new injection passes through all three phases so that at any moment the rate of disappearance after a second injection is the sum of the rates at that moment for each injection.

Based on these considerations, Lawson and his colleagues tested a dye decrement method. Calculating the blood volume from the curve following injection of undyed plasma into dyed animals, they find values about 85 per cent of those by Gibson-Evans (12) method. The discrepancy is greater when the early disappearance is rapid. Lawson's group studied total cell volume of arterial blood by combining hematocrit values with estimates of blood volume by either dye injection or dye decrement and also by the change in the arterial hematocrit after injection of plasma or cell-concentrates. The usual measurements of cell volume are probably 40 per cent too high partly because the dye injection method may give falsely elevated plasma volumes and partly because the arterial hematocrit gives too high a value for total hematocrit. Moore, Shadle & Lawson (234) injected red cells tagged with methemoglobin into splenectomized dogs. Determinations of cell volume from methemoglobin measurements agreed closely with those calculated from hematocrit change.

Nizet (13) measured blood volume using 20 to 50 cc. of blood labelled by treatment with phenylhydrazine which produces Heinz granules in the erythrocytes.

Blood volume in children.—Morse *et al.* (14) estimated the

blood volume of 77 normal children, 1 to 17 years of age, by the Gibson-Evans method. Prediction formulas based on height, weight, and chest girth give plasma volume with a standard error of estimate of the mean of 8.5 per cent. Whole blood may be predicted with a slightly greater precision. Since the methods for blood volume determination differ in their estimates by about 15 per cent, the reliability of blood volume estimation is sufficiently uncertain to necessitate extreme caution in interpreting individual deviations from a "norm." Probably the tolerance allowed should be greater than these carefully collected data taken in uniform conditions suggest.

The distribution of blood volume.—Nylin (15) measures the circulatory blood volume of different parts of the body using tagged erythrocytes. These are injected while the part under study is kept ischemic and then again after its circulation is reestablished. This gives the volume of cells trapped in the organ by the occlusion. One lung during pulmonectomy contains 17 per cent of the total circulating blood volume. The lower limbs contain 13.6 per cent. Thompson & Rockey (16) have used tracer substances to estimate the "speed" of pulmonary circulation effected by artificial pulmonary inflation.

Shock and Hemorrhage

The reader is referred to the careful and detailed report of the Conference on Hemorrhage organized by the New York Academy of Sciences (17).

Gregersen and his school (18, 19) emphasize the similarities and differences between hemorrhage and shock as seen in the experimental laboratory and in man. They point out the large diminution in cardiac output in shocked dogs (20) and the evidences of stagnant tissue anoxia (21).

Overman, Wang & Painter (22, 23) have studied the evidence that afferent impulses in traumatic shock acting reflexly through the sympathetic nervous system may, by vasoconstriction, accentuate tissue anoxia so that the traumatized animal is more sensitive to blood loss than the normal one. Shocked dogs bled to death had an increase in residual blood in the inferior caval territory and a decrease in the superior cava and azygos area. This led Foreman (24) to stress the increased splanchnic capacity as the reason for the sensitivity of shocked animals to small hemorrhages.

Liver and kidney.—Shorr, Zweifach and associates continue detailed observations on hepatorenal factors in circulatory homeostasis. They (25, 26) attempt synthesis of many of these observations into a tentative picture of their part in shock. When blood loss, fluid loss, or failure of general venous and capillary tone directly or reflexly produce a true renal ischemia, anerobic processes rapidly form and release VEM (vasoexcitatory material). VEM tends to direct the blood flow through direct thoroughfare channels. During this phase the liver does not form VDM (vasodepressor material) but retains its capacity to destroy it and to inactivate VEM but not as fast as VEM is being produced. VDM is being slowly produced in skeletal muscles, but its effect is probably insignificant since it is subject to destruction by the liver and to neutralization by VEM. This stage of hyperreactivity passes gradually into a hyporeactive stage in which increasing amounts of VDM appear in the blood stream and the terminal metarterioles become quiet and unreactive. Blood is diverted to capillary venules and stagnates. Hepatic anoxia starts anerobic metabolism in the liver with rapid production of VDM and progressive deterioration and failure of the VDM inactivating mechanisms. Because of this failure to inactivate VDM, transfusions at this stage are unsuccessful since VDM continues to accumulate and the transfusion fluid or blood continues to accumulate and stagnate in the venules. The kidney loses its capacity to form VEM and as urine formation fails the clearance of VDM decreases.

The authors regard the hepatorenal-vasotropic mechanism as a normally acting homeostatic device in which VEM formation and the production of VDM and its destruction or elimination are nicely balanced. During hemorrhage the production of VEM in the hyperreactive state is a compensatory mechanism which is usually successful. When it fails, shock becomes irreversible primarily because of insufficient oxygen supply to the liver.

These concepts are very closely reasoned on experiments which have for their fundamental basis the change in the response of the vessels of the rat's mesoappendix to standard doses of epinephrine when these vessels are under the influence of the various tissue extracts involved, and the reader is referred to the original report to follow the analysis. Chambers & Zweifach (27) further report on the VEM-VDM sequence in hemorrhage, tourniquet, and traumatic shock.

Wilhelmi & Long (28) stress the importance of adequate blood and oxygen supply to the liver in maintaining its capacity to destroy the vasodilator material which plays a key part in the terminal vascular collapse of shock. The liver has considerable tendency to regain this capacity rapidly when its oxygen supply is adequate.

Phillips *et al.* (29) describe the renal circulatory events early in hemorrhage. Peripheral vasoconstriction occurs first while the kidney blood flow is favored; next comes a phase of markedly diminished renal blood flow in which the filtration rate is maintained by efferent arteriolar constriction; then the afferent glomerular vessels constrict, the glomerular filtration falls off, and the renal blood flow approaches zero. All these events occur before the central arterial pressure, as a result of the hemorrhage, falls dangerously low and while the hemorrhagic state is still surely reversible.

Burn shock.—Blood from burned dogs transfused into normal dogs had more vasodepressor effect and produced a greater mortality than blood from normal dogs according to Giraldi, Peterson & Cole (30).

Traumatic shock.—After trauma to muscle, Cleghorn (31) found the effectiveness of transfusion was not increased by giving more than 45 per cent of the blood volume. Drinking water after a transfusion increased survival rate. Dogs transfused after the arterial pressure was down to 70 per cent of its normal level rarely survived. Desoxycorticosterone acetate (DCA) did not increase survival rate but carbohydrate-active cortical extract seemed to help. Cleghorn, like others, found traumatized dogs sicker than bled ones at corresponding arterial pressure levels. Suppression of urinary function did not contribute to death, but impairment of the renal pressor mechanism and adrenal cortical function may be important.

Henry and co-workers (32) find no change in capillary permeability with mild anoxia, but in extreme anoxia with venous blood less than 25 per cent saturated a significant increase in permeability to protein occurs immediately.

Little, Green & Hawkins (33) showed that trauma from ischemic compression of the limbs of dogs produced cessation of urine flow only in the traumatized member of a pair of cross transfused dogs, but when the arterial pressure was lowered an equal amount the two dogs both became anuric. Bobb & Green (34) feel that the kidney does not affect the survival in ischemic compression

shock. Nor is compression shock due to local edema according to Lipton, Denison & Green (35). Local and environmental cooling both protect against such shock.

Crush syndrome.—Goormaghtigh (36) finds the renal lesions in fatal crush wounds and traumatic uremia are identical with those of fulminating glomerulonephritis or eclamptic anuria. Corcoran & Page (37) analyze the crush syndrome and indict vasoconstrictive renal ischemia and a hypothetic toxic agent. The oliguria and aciduria contribute to the obstruction by precipitation of myohemoglobin and methemoglobin within the tubules. Harrison *et al.* (38) find that methemoglobin produces more severe renal injury than oxyhemoglobin.

Gibson *et al.* (40) found circulating blood volume reduction in hemorrhage greater than blood loss. They attribute this to stasis of blood such as occurs in the minute vessels of all the organs in all tyyes of shock. Root, Walcott & Gregersen (41) present relationships between various measurements in muscle shock quantitated according to the percentage reduction in blood volume and compare them with hemorrhagic shock. Arterial wave forms during hemorrhagic shock were studied by Alexander & Webb (39). Harris (42) compared electrocardiograms of experimentally shocked animals with those of patients in hemorrhagic shock and found essential agreement.

Comparing infusion fluids for treatment of hemorrhage in dogs, A. S. Hamilton, Parkins & Waltzer (43) found them increasingly effective in the following order: globin, saline, hemoglobin, oxypolgelatin, 25 per cent albumin, 5 per cent albumin, plasma. They emphasize the special precautions necessary to prepare plasma optimally. These precautions may prove useful in increasing the activity of blood-perfused isolated organs. A parallel study from the same laboratory [McCarthy & Parkins (44)] showed that saline was as effective as any other fluid tried in promoting the survival of scalded rats. Hemoconcentration and plasma volume do not appear to these authors to be critical factors in recovery from this type of injury.

P. B. Hamilton, Hiller & Van Slyke (45) replaced blood with 7 per cent hemoglobin. Immediate results were satisfactory but there was evidence of the delayed temporary renal impairment.

Green & Metheny (46) advocate testing hemorrhage patients on the tilt table and quantitating their transfusion requirements in accordance with the degree of their failure to adapt to tilting.

Blood clotting.—With the addition of peptone to the perfusion fluid of the isolated liver of the dog no heparin is liberated [Rocha e Silva *et al.* (47)]. This confirms the authors' recent claim that the liberation of heparin in peptone shock involves more than a liver mast cell response.

Emphasis is placed by Ferguson (48) on the part played in coagulation by an important accessory factor in the conversion of prothrombin to thrombin as reported by others (49 to 52). Ware, Guest & Seegers (53) term this material Ac-globulin and find that in high concentration it can compensate for low prothrombin concentration and hasten clotting. They (54) find Ac-globulin activity greater in serum than in plasma. Thrombin is required for the production of serum Ac-globulin from plasma; calcium is not. Sykes, Seegers & Ware (55) consider that the pronounced and rapid decrease in Ac-globulin which follows acute hepatic damage by chloroform suggests that the substance is formed in the liver.

Circulation Time

A good critical analysis of the use of thiamine and other techniques for measuring circulation time is offered by Ruskin & Decherd (56), who conclude that while it is a useful measurement and their method gives adequate results, the ideal method is yet to be found.

Wilburne and associates (57) determine circulation time with acetylcholine using cardiac asystole as the end point. They have studied man and the dog, the latter having a circulation time of 7 sec. Rodbard & Fink (58) find that in the chicken, following injection of acetylcholine, lowered arterial pressure precedes cardiac inhibition.

Winsor and co-workers (59) use riboflavin as a fluorescent tracer for circulation time measurements. They emphasize the possibility of exploring different regions of the body and the advantage of being able to include in their measurements long arterial pathways to the foot. Circulation time measured by a calcium-magnesium mixture gives a wide spread in the distribution of normals, but Meneely & Segaloff (60) could not relate the normal values to height, weight, age, season, or pulse rate. This encourages skepticism about the usefulness of circulation time measurements, except perhaps in highly specialized and well-controlled studies.

Hepatic Blood Flow

Myers (61) examined the possibility of estimating the blood flow through the liver by applying the Fick principle to the measured urea elimination and the difference between the arterial and venous hepatic blood urea concentration. This method gives figures close to those of the bromsulphonphthalein (B.S.P.) method but is said to be difficult and of doubtful soundness because of the small arteriovenous differences, uncertainty as to the uniformity of distribution of urea, and the possibility of unpredictable renal effects. The danger of equating urea elimination to urea production in dogs under basal circumstances has been stressed by Ogden & Tripp (62). The liver uses about one quarter of the total oxygen consumption (61). According to Munnell & Taylor (63) the effective hepatic blood flow (EHBF) is unchanged in pregnancy.

Cirrhosis of the liver, regardless of etiology, has little if any lowering effect on EHBF [Bradley *et al.* (64)] but the hepatic arteriovenous oxygen difference is usually increased. Pyrogens [Bradley & Conan (65)] increased EHBF up to 300 per cent and decreased B.S.P. extraction ratio irrespective of whether the fever was controlled by amidopyrine. Wilkins, Culbertson & Ingelfinger (66) find EHBF normal in hypertension. Splanchnicectomy must reduce the vascular resistance of the liver since it increases EHBF unless there is a definite fall of arterial pressure. The total elimination of B.S.P. is decreased. This group (67) further reports that the upright posture lowers EHBF. Splanchnic vasoconstriction occurs in the upright position, since the decreases in blood flow could not be accounted for by significant changes in blood pressure,

Circulation in the Extremities

Panzer and co-workers (68) describe a simply assembled electromagnetic sphygmograph which records on a smoked drum; and Berry *et al.*(69) describe a compensation plethysmokymograph for measuring blood flow in human extremities.

The blood flow through the extremities, long studied from the standpoint of temperature regulation, is receiving much attention now. Positive pressure breathing may displace half a liter of blood into the veins of the legs and abdomen according to Fenn *et al.* (70) who note that this phenomenon is accompanied by constriction of the arteries in the feet. These phenomena are separable and are

believed to be reflex; so also is the decrease in finger pulse volume and blood flow observed in similar circumstances by Fenn & Chadwick (71). Gilliatt (72) has evidence that reflex vasoconstriction in the finger on inspiration depends upon wide chest or lung movements rather than negative pressure or changes in systemic arterial pressure. Abdominal breathing elicits the reflex only if inspiration is rapid. While the site of the afferent endings was not determined, studies on paraplegics by Gilliatt, Guttmann & Whitteridge (73) indicate that it is a spinal reflex with afferents entering the cord in the upper thoracic region.

Hertzman, Crandall & Jochim (74) emphasize the part played by the venules in producing changes in cutaneous blood content and color independently of blood flow. The content and flow of blood in the pad of the finger usually vary together, but in the forearm and still more in the brow the vasomotor discharges predominantly affect content rather than the flow. Thus the temperature of the finger pads is highly labile compared to that of the brow. The changing volumes of blood in the skin, measured by the photoelectric plethysmograph, are 30 to 40 cc. per man. Therefore this method is not measuring the changes in the "currently taught" blood reservoir of the skin.

Physical and chemical effects on vascular system of extremities.— Halperin, Friedland & Wilkins (75) showed that a local pressure of 20 mm. Hg may impair cutaneous circulation. Wilkins (76) also found that the blood flow may be increased without production of edema by alternating dependency and elevation of an extremity. Scheinberg *et al.* (77) showed that, when the blood pressure in the foot is doubled by standing, the blood flow increases without compensatory vasoconstriction.

Epinephrine was injected intra-arterially in man and its effect on the blood vessels in the forearm was estimated by Harpuder, Byer & Stein (78) from plethysmographic measurements of blood flow. Doses from 0.0002 μg. to 0.05 μg. increased blood flow so immediately as to indicate vasodilation rather than a general rise of arterial pressure. Doses from 0.1 to 0.5 μg. were ineffective, and doses from 1 to 2 μg. lowered blood flow without evidence of widespread effect. During the hyperemia induced by occlusion, exercise, or intra-arterial histamine, the constrictor doses of epinephrine are ineffective.

Ingestion of 20 gm. of glycine [Gubner, DiPalma & Moore

(79)] raised oxygen consumption, surface temperature, and blood flow. This was compared with the skin hyperemia produced by posterior tibial block and by whiskey (79). Similarly Roth & Sheard (80) were able to maintain elevated temperature in the extremities by giving a substantial meal (500 to 800 kilocal.) every one and a half to two hours. This was accompanied by a three- or fourfold increase in the metabolic rate.

Scheinberg and co-workers (77) made the curious observation that the time necessary to produce maximal blood flow by arterial occlusion at 32°C. is much greater in the lower extremity than that previously reported in the upper extremity. This may be compared with the observation (81) that the responses to intradermal histamine in the warm extremity are much delayed in the foot as compared with the arm.

Nervous factors.—Kemp, Tuttle & Hines (82) observed that denervation of the dog leg causes an immediate twofold increase in blood flow through the limb. As muscle atrophy progressed the blood flow diminished to about three quarters the flow through the sound limb. Hingson & Southworth (83) advocate continuous spinal or caudal anesthesia as a means of raising the blood flow for diagnosis and treatment of peripheral vascular insufficiency. Collins, Foster & West (84) review the vasomotor disturbances in poliomyelitis and note that they are common during convalescence and may often be relieved by sympathetic nerve block.

A careful study of the effect of heat applied to one extremity on the blood flow and temperature of the heated and unheated extremities was made by Ferris *et al.* (85). They observed that the person in cool surroundings shows little change in the vascular status of one extremity when the other one is heated, but at room temperatures, from 21 to 25 degrees, warmth applied to one extremity caused vasodilation in the other. This adds to the demonstration that between the metabolic and environmental balance producing extreme vasodilation and that causing generalized peripheral constriction is an intermediate stage where the peripheral vascular system is highly labile. For persons in the basal state this balance of equilibrium is between 21°C. and 25°C., and for this reason dilation tests for vasospasm should not be conducted at temperatures above 20°C.

The dilation of the blood vessels of the extremities which results from wrapping and warming the whole patient includes a dilation

of blood vessels in muscles. Barcroft, Bonnar & Edholm (86) believe in these circumstances the muscles may take an extra liter and a half of blood. This dilation in the muscle can be measured when the skin vessels are flushed by mustard or when they are constricted with epinephrine. The increase in blood flow per gram of muscle produced by warming the body is only one twelfth of that produced by exercise and one tenth of the increase which warming induces in the skin vessels.

Vascular disorders of the extremities.—Abramson & Schumacker (87) note that Reynaud's disease occurs as commonly in men as in women, though in men the emotional precipitants of the phenomenon are less evident.

Johnson (88) finds that the intravascular clotting characteristic of frostbite does not occur until four or five hours after the trauma and plans trying the immediate use of heparin in an attempt to prevent gangrene by the inhibition of intravascular clotting. Studies in the rabbit by Lange, Weiner & Boyd (89) emphasize the differences between frostbite and immersion foot. While in the latter there is usually no stoppage of blood flow, they believe the lesions to be due to prolonged hypoxia resulting from intense vasoconstriction. At the temperatures obtaining during the production of immersion foot, the rate of oxygen dissociation is decreased and this may contribute. Degenerative changes in nerve tissue and electrocardiographic changes are reported. Brown, Wise & Wheeler (90) found that moderate cooling of the forearm (*a*) increased the extravascular volume of the forearm; (*b*) decreased the rate of filtration produced by a given rise of venous pressure; and (*c*) decreased the rate of reabsorption of intravascular fluid. This may, in part, be attributed to increased capillary permeability particularly with respect to protein. Cold, by producing arteriolar constriction and increased capillary permeability, sets into operation two opposing forces, hydrostatic and osmotic, in such a way that adequate tissue fluid formation may take place with a small blood flow. Because of the decreased reabsorption, due both to protein leakage and probably reduced capillary surface, edema will form readily when cold, as in immersion foot, is reinforced by the increased venous pressure of dependency. This occurs despite the fact that moderate increases of venous pressure do not increase filtration rate so much in the cold limb with constricted vessels as they do in the normal limb.

Veins

In an extensive analysis of the gross anatomy of the venous system Herlihy (91) stresses the importance of the vertebral plexuses. He claims that the usual discussion of the veins fails to emphasize the free communications which facilitate venous drainage into this large store from the head, neck and limbs, thoracoabdominal walls, pelvis, and various viscera. The storage capacity of these veins is in excess of 200 cc. and their position makes them important in adjustments to rapid changes of thoracic, abdominal, intracranial, and surface pressure.

Bradley & Bradley (92) reported on renal function in persons subjected to an abdominal pressure cuff inflated to 80 mm. Hg which raised the intra-abdominal venous pressure to 20 mm. Hg. Average reductions of 24 per cent *p*-aminohippurate (PAH) clearance and of 27.5 per cent inulin clearance appeared. PAH extraction ratios of 90 to 96 were observed with no difference between those under abdominal pressure and the controls. The diodrast *Tm* was always depressed; the glucose *Tm* sometimes. In a discussion of the significance of these data the authors suggest that since tubules of different lengths may have different resistances, the "low pressure" nephrons may be blocked by a raising of the pelvic pressure to a degree which is insufficient to block the flow in other nephrons. This concept seems to imply that the "low pressure" nephrons, in addition to having a different resistance, must have a different pressure differential between their Bowman's capsules and their collecting tubules since it is only when the two ends of a tubule are at identical pressure that the flow can be expected to cease.

Booker, French & Molano (93) discuss the cardiovascular and respiratory effects of minor increases in abdominal pressure and point out that these may result from internal distension as readily as from outside pressure.

Altschule, Freedberg & McManus (94) note a progressive dilation of the small blood vessels of the finger nail fold during intravenous infusions, together with a greatly accelerated blood flow and a markedly increased cutaneous lymph flow.

Mackay (95) analyzing the jugular pulse suggests that the *a* wave is of venous origin and the *c* wave partly venous and partly arterial.

A considerable volume of work has appeared dealing with venous pressure in its relationship to heart failure and cardiac filling, some of which is considered in the chapter on heart in this volume.

Slocum, Hoeflich & Allen (96) describe the untoward cardiovascular effects of extreme positions on the operating table and analyze them physiologically. Slocum, O'Neal & Allen (97) offer a similar discussion of neurovascular injuries.

The effects of gravity.—The pressure in the cerebrospinal fluid and the venous system, measured at heart level, change together in a varying gravitational field, and Rushmer, Beckman & Lee (98) point out the protective value of this arrangement. Britton *et al.* (99) studied accelerations up to 50 g and reported carotid pressure down, femoral pressure down, heart rate up at first and later down. Immediate slowing or stoppage of carotid blood flow was noted. An abdominal cuff inflated to 300 mm. Hg pressure offered considerable protection. Van Middlesworth & Kline (100) find 13 per cent carbon dioxide protects against 6 g as well as an abdominal cuff inflated to 300 mm. Hg.

Studying the postural vascular dynamics of semistarved people, Taylor, Henschel & Keys (101) found that additional stresses seem to make the difficulties of the erect posture more serious. "Among the stresses which might well result in syncope in the starved individual 'queuing up', we may mention hot weather, dehydration as the result of diarrhoea, and respiratory infections." Tilt-table fainters seem to improve with starvation.

Vascular System in Pregnancy

Reynolds (102) shows a decrease in somatic circulation rate of rabbits early in pregnancy followed by a transient increase. The rate also decreases in the parts of the gravid uterus immediately surrounding the conceptus. The circulation in the nongravid horn of a unilateral pregnancy is unchanged and that in the interconceptus sites is the same in the second trimester of pregnancy as in the nongravid undistended uterus. The interpretation of local blood velocities is difficult because the two components, increased vascular cross section and increased delivery of blood, tend to affect circulation velocity in opposite directions. The same author (103) discusses the possible significance of the spiral artery in the rabbit's ovary and suggests that it may serve for the extension in

length which the ovary undergoes and also serve to diminish arterial pressure. He makes no mention of the likelihood that such an arrangement would tend to produce a steep gradient in pulse pressure and convert the pulsatile arterial flow into a flow more nearly of the capillary type. Changes in the architecture of the spiral artery occur under the influence of gonadotrophic substances (104, 105).

The physiologic changes in the circulation during and after obstetric labor seem to Brown and associates (106) to be essentially those of the obliteration of a large arteriovenous shunt. The intermittent occlusion of this shunt by the uterine contractions of normal labor may serve to prepare the cardiovascular system for this change.

Arteriovenous anastomoses in the liver, spleen, and lungs were studied by Prinzmetal *et al.* (107) through intravenous injection of glass microspheres (10 to 440 micra). Recovery of the spheres by digestion of the tissues in alcoholic potash and measurement under a microscope revealed that the arteriovenous pathways of the liver attained a diameter of 180 micra while those of the spleen and lungs reached 370 and 390 micra respectively.

Arterial Pressure

Methods.—Laboratory methods for the measurement of arterial pressure reported include a cylindrical wire strain gauge (108) and a variable capacitor (109). Various workers have been using new types of manometer during the last few years but there is no systematic comparative evaluation of their relative merits.

Kersten *et al.* (110, 111) have devised and tested a method for measuring rats' arterial pressure by a leg-cuff and photoelectric plethysmograph. The method has the advantage that neither the animal nor the extremity need be heated or anesthetized. Chittum, Hill & Grimson (112) describe an acoustical end point detector for rat arterial pressure measurement. The tail plethysmograph method has been adapted for the mouse by Wu & Visscher (235).

The flexible catheter continues to snake its way into new passages—via the carotid artery, aorta, left heart to the pulmonary vein in the dog (113) and into the coronary sinus and middle cardiac vein of man (114). The portal system is still inviolate.

Normal values.—Boynton & Todd (115) analyze the arterial pressure of 75,258 persons at the University of Minnesota Student

Health Service. Mean pressures were: men, 122/74.5; women, 111/69.7. The diastolic pressure rose with age in both sexes; the systolic only in women. Currens (116) studied the influence of postural change on the arterial pressure of men and women (500 of each). Four per cent had a diastolic hypertension in the erect posture. This was more commonly encountered in males than in females, the proportion being 3.5 to 1. Schaposnik (117) finds a definite relationship between arterial pressure and anthropometric build.

Experimental Hypertension

Renal pressor substances.—The relation of renin to experimental hypertension is still the subject of much study. A review of the literature (118) suggests that there is a strong case in favor of the renin mechanism being at least partly responsible for the initiation of experimental renal hypertension, but that there is insufficient evidence that renin plays a major part in the maintenance of chronic hypertension. Haynes & Dexter (119) find renin early in experimental hypertension but after a week it begins to diminish and then disappears. They consider three hypotheses: the hypertension may be caused by products of autolysis of the kidney resulting from sudden reduction in its blood supply and the renin found may be purely incidental; alternatively the hypertension may be initiated by renin and subsequently maintained by some other mechanism as suggested by Ogden *et al.* (120), or yet again the sensitivity to renin may change and hypertension may be maintained by concentrations of renin too small to be measured by present techniques.

The whole question of the part played by renin in the normal and abnormal physiology is reopening with the realization that hypertensin apparently needs minute quantities of epinephrine, tyrosine, or other tissue products to make it effective (121). This may explain some of the curious phenomena reported by Tripp & Ogden (122) and by Page (123). Renin and angiotonin are not destroyed by perfusion through the rabbit heart [Trautman, Davis & Findley (124)].

In the course of studies on shock, Shorr (26) and his colleagues have made extensive studies on a vasoexcitor material (VEM) which seems similar to but not identical with angiotonin. In experimental renal hypertension VEM in the peripheral blood

occurs in about the same circumstances as those in which other authors find renin. With a marked clamping it may be found in thirty minutes. Ordinarily it rises to a maximum during the first week while the hypertension is becoming established, and after a few weeks during persistent chronic hypertension VEM seems to disappear from the blood. The kidneys of a hypertensive dog incubated *in vitro* will continue to make VEM even during the chronic stage. The seeming disappearance of VEM from the blood stream as hypertension progresses is due to the fact that VDM concentration in the blood stream rises and neutralizes the excitor material. The relationship between this hepatorenal mechanism and the renin-angiotonin system is not clear.

Helmer & Shipley (125) and Schroeder (126) have recently described two more pressor substances which are manifest in somewhat similar circumstances. Shipley & Helmer (236) report the specificity of their sustained pressor principle to be like that of renin. Mylon *et al.* (127) point out the uncertainty of our present knowledge of "the renin hypothesis" but it seems that the time is not yet ready for a clarification of the relationship between these various "pressor manifestations." Shipley & Tilden (128) assay pressor substances on a pithed rat.

Gollan, Richardson & Goldblatt (129) purified a plant hypertensinase. The extract is not absorbed from the muscles but large intravenous injections caused an immediate fall of arterial pressure in dogs. Three thousand units of this substance rendered a hypertensive dog normotensive for four hours. It was not stated whether the animal suffered from acute or chronic hypertension.

Lewis & Page (130) found little change in the plasma proteins in essential hypertension. Hypertensive dogs on the other hand had an increase in γ-globulin. Malignant hypertension in dogs and man was accompanied by a rise in β-globulin.

Neurohypertension.—Forster & Maes (131) raised the arterial pressure of rabbits in acute experiments by section of the depressor nerves and clamping the carotid sinuses. A rise of blood pressure was accompanied by a disproportionately small increase in clearance of *p*-aminohippurate and a disproportionately large increase in creatinine clearance. By conventional interpretation this would indicate a marked rise in renal resistance situated predominantly in the efferent glomerular vessels. Such an effect might be mediated by the direct release of the inhibitory effect which the carotid and

cardioaortic zones ordinarily exert on the sympathetic tone of renal blood vessels or else by the release of renin which might be expected to result from increased sympathetic tone and cardiac acceleration (132). On the other hand at present renal clearances should be interpreted with great caution, especially in the rabbit, since the observations of Trueta *et al.* (133) suggest that the vascular system of rabbit kidneys may not behave in the fashion currently attributed to the kidneys of other species.

Kottke, Kubicek & Laker (134), extending their observations on hypertension from excitation of the renal nerves, note that the hypertension lasts only during the excitation and may not be accompanied by a decrease in renal blood flow. Diathermy applied to the back or the head of normal or hypertensive man produces a decrease of renal blood flow without a change in systemic blood pressure.

Endocrine hypertension.—Friedman & Friedman (135) find enucleation of the eyes in rats produces hypertension, cardiac hypertrophy, and increased renal blood flow with no evidence of other renal disturbance.

They [Friedman, Polley & Friedman (136)] find also that desoxycorticosterone raises arterial pressure, lowers renal blood flow, raises the filtration fraction, and raises the Na to Cl ratio. A rise of arterial pressure in hypertensives but not in normotensives after administration of desoxycorticosterone is reported by Perera & Blood (137). The rise is not ascribed to salt or water retention since while this occurred in both groups only the former showed an increase in blood pressure. Manipulation of salt in the diet produced corresponding changes in the blood pressure of hypertensives, but DCA was effective only when the salt intake was high. The syndrome of hypertension and nephrosclerosis produced in the rat by injection of lyophilized anterior pituitary [Prado, Dontigny & Selye (138)] is prevented by low protein diets in contrast to that produced by DCA.

Sobin & Landis (139) showed that the renal lesions produced by choline deficiency are not accompanied by hypertension. Abrams & Sobin (140) report that rats may readily be rendered hypertensive by wrapping the kidneys in molded latex capsules and Zbinden (141) finds capsules of cellulose acetate effective.

Grollman (142) observes that the fall in blood pressure in hypertensive animals during pregnancy is less common in the larger

species. When it occurs it does not appear to be due to hormonal factors.

Wastl (143) claims possiblities in the alleviation of human hypertension for corn-silk extract which lowers the blood pressure of hypertensive rats without adverse effects being observed.

Hypertension in Man

Sympathectomy.—Reports continue to appear attempting to evaluate sympathectomy as a treatment for hypertension. Cooke & Barclay (144) report encouraging results after 12 to 40 months in eight out of ten patients whose retinae were graded 2 and 4 on the Keith-Wagener scale. Improvements were noted in symptoms, eye grounds, and blood pressure, while *Tm* and the ratio of clearance to *Tm* remained unaffected. The authors therefore doubt that the kidneys were primarily concerned in the etiology of their cases. Poppen (145) describes a new technique for extensive sympathectomy.

Hypertensives with clinical and pathological signs of renal disease respond well to splanchnic nerve section according to de-Takats & Fowler (146), but neurogenic hypertension is mediated by a hypothalamic-pituitary mechanism rather than by the sympathetic nervous system. Essential hypertensives after lumbodorsal sympathectomy had a transient decrease in blood volume and a rise in thiocyanate extracellular fluid space [Freis & Smithwick (147)].

Landowne & Alving (148) believe that low renal resistance predicts a favorable outcome for sympathectomy. Birchall *et al.* (149) studied the effects of tetraethylammonium on 16 hypertensive patients of whom 12 were later sympathectomized. Fall of arterial pressure, mydriasis, peripheral numbness and tingling, and ptosis of the lids were caused by smaller doses; larger doses produced dry mouth, muscular weakness, nasal congestion and finally curariform effects, dysarthria, dysphagia, and intercostal paralysis. They attribute the effects to relative depression of the autonomic nervous system, stimulation of the peripheral sensory nerves, and curariform action. Their results suggest that the drug is of no value in selection of patients for sympathectomy.

The kidney.—Oster (150) and others call attention again to the possibility that unilateral renal disease may be responsible for more hypertension than is currently thought. One additional case

of cure of hypertension by unilateral nephrectomy is reported by Hardwick & Badenoch (151).

Haynes, Dexter & Seibel (152) have a technique for determination of renin in normal and hypertensive patients. Finding no difference between hypertensive patients and controls, they suggest the possibility that the procedures incident to renal vein catheterization may cause the liberation of renin.

Several cold pressor tests during pregnancy are advocated by Krieger & Weiden (153) since the chance of the occurrence of preeclamptic toxemia increases with the number of hyperreactive responses given by any patient. Talso, Crosley & Clarke (154) show renal vasoconstriction from the cold pressor test.

Bradley *et al.* (155) found increased pulse rate and stroke volume with lowered peripheral resistance in patients with pyrogenic reaction from typhoid vaccine even though they had been protected against fever by preliminary doses of amidopyrine. The arterial pressure of normotensives was unaffected but in three out of six hypertensives there was a fall of arterial pressure to normotensive levels or below. Renal blood flow increased both absolutely and relatively.

The basal metabolic rate is elevated in proportion to the arterial pressure, according to Rosenkrantz & Marshall (156). They speculate upon its cause and point out that the carbon dioxide tension in expired air is normal. From this they infer that these persons need hypertension to maintain adequate circulation through brain and lung; Frances Selye (157) on the other hand finds an increased carbon dioxide combining power in hypertensives. Ammonium chloride improves these patients and one might imagine therefore that they "need" a higher carbon dioxide tension and that the normal carbon dioxide tension found represents a failure of adjustment—perhaps a failure to adjust to the relative sodium retention which Selye finds in these patients.

Taylor, Corcoran & Page (158) offer good evidence that ovarian failure does not cause hypertension at the menopause. Hinchey, Hines & Ghormley (159) found osteoporosis in 2 per cent of hypertensive patients treated with potassium sulfocyanate. It was resistant to all treatment but withdrawal of the drug.

Heinbecker (160) advances the theory that essential hypertension is due to a functional depression of the neurohypophysis which sensitizes the blood vessels to the action of renin, epineph-

rine, and desoxycorticosterone; later, owing to the effect of increased intracranial pressure on supraoptic and paraventricular nuclei, the disease becomes organic rather than functional. Hypertension is regarded by Heinbecker as the reaction of the body to any inadequacy of renal tubular function. It is part of the mechanism for compensating with increased blood flow the deficiency of the renal tubular mass.

Atherosclerosis and Arteriosclerosis

The *sine qua non* of atherosclerosis [Moreton (161)] is the presence in the circulating blood of coarsely suspended colloidal particles considerably larger than those found in normal plasma and composed of or containing a substance relatively resistant to the resorptive and removal mechanisms of the arterial intima (macrophages and tissue fluid enzymes).

Gordon (162) studying the mechanism of lipophage distribution in atherosclerosis believes the lipophage cells penetrate the intima under the pressure gradient and are stopped by the elastic tissue of elastic arteries. In other vessels they continue on and return via the lymphatics. Therefore arteriosclerosis does not occur in capillaries and veins.

Boas, Parets & Adlersberg (163) studied 122 patients under 50 years of age with proved coronary atherosclerosis and serum cholesterol above 300 mg. per 100 cc. In these patients one-third to one-half the families showed hypercholesteremia.

Rabbits on high cholesterol and polyoxyalkylene sorbitan monooleate (Tween 80) showed extreme hypercholesteremia and early severe atherosclerosis [Kellner, Correll & Ladd (164)]. Dogs showed a similar effect from thiouracil [Steiner & Kendall (165)]. Blumenthal (166) believes arteriosclerosis to be a fibrosis of the vessel walls due to anoxemia.

A critical analysis by Buck (167) on the etiology of atherosclerosis concludes that neither the hemorrhage-anoxia-fibrosis hypothesis nor the lipoid deposition hypothesis is alone adequate. He highlights our ignorance of the precise response of the endothelial cell to cholesterol.

Chemical Agents

Endocrines.—De la Barreda, Diaz & de Molina (168) find a vagopressor reflex active after hypophysectomy, adrenalectomy,

nephrectomy, and hepatectomy. The blood of dogs during this elevation of pressure contains a pressor substance as shown by crossed-circulation experiments and the perfused frog. The effect is abolished by section of the medulla but not by ergotamine.

Adrenal cortex.—Goldman & Schroeder (169), testing the immediate pressor effect of intravenous desoxycorticosterone acetate (5 mg. in 2.5 ml. propylene glycol) on normotensive and hypertensive persons, found little or no effect in normals but a marked pressor effect in hypertensives. The response lasted for more than thirty minutes. There was no increase in ballistocardiographic thrust nor were there electrocardiographic changes. Perera (170), however, challenges the claim that intravenous DCA causes any immediate pressor effects.

Kidney.—In the "endocrine kidney" according to Kochakian & Dontigny (171) arginase and alkaline phosphatase are nearly absent. Acid phosphatase decreases in amount but not in concentration. The juxtaglomerular apparatus is frequently absent in such kidneys and therefore Selye (172) concludes that this structure is not essential for the production of renal hypertension.

Mylon & Heller (121) noted that hypertensin and 20 amino acids were all without effect on the perfused rabbit's ear but that traces of epinephrine would activate hypertensin and tyrosine but did not activate the other substances tested. Many tissue extracts which seem to have no vasoactivity become highly active in the presence of epinephrine or plasma containing epinephrine (173 to 175). These observations are of particular interest in view of the use of epinephrine in all assays of VEM and VDM.

Edman (176) has made a detailed study of the purification and properties of hypertensin. The yield from one ton of horse blood is 30 mg. of a preparation, 1 mg. of which has a pressor activity equal to that of 39 mg. tyramine acid phosphate. This represents about 3 per cent of the amount obtainable from all the substrate in the plasma. It is essentially pure with an isoelectric point at pH 6.8, a probable molecular weight of around 2,700, and contains lysine, histidine (28 per cent), glycine, alanine, serine, proline, valine, tyrosine, leucine (or isoleucine), and aspartic and glutamic acids.

Adrenal medulla.—The output of epinephrine from the perfused adrenal gland is increased if the flow decreases or if the oxygen content of the arterial blood is low according to Bülbring,

Burn & de Elio (177). The discharge obtainable by splanchnic nerve stimulation depends upon the amount in the gland. The finding that epinephrine constantly increases the filtration fraction and inconstantly diminishes urine flow was confirmed by Barclay, Cooke & Kenney (178), who find no evidence that epinephrine plays a significant part in the renal picture seen in exercise.

Drugs affecting autonomic nervous system.[2]—McDowall (179) notes that the potentiating action of acetylcholine or epinephrine which is observable in heart, blood vessels, arterial pressure, pupillary and intestine muscles, and also in the perfused hind limb is probably local and peripheral; the cholinergic organs most active just before an emergency arises are therefore most ready to respond when epinephrine is secreted.

A sympathomimetic substance extracted from brain by Raab (180) is termed encephalin. It affects the arterial pressure like epinephrine and its pressor action correlated well with its colorimetric estimation. Cocaine, however, does not affect the response to encephalin. Ergotamine and dibenamine weaken its action but produce no inversion. Its action, diminished by decerebration or pithing, is like that of epinephrine on the rabbit heart and intestine although comparatively stronger and longer lasting on the pupil and weaker on the uterus. Encephalin is not so easily oxidized by iodine nor, unlike epinephrine, is it destroyed by ultraviolet radiation. While its absorption and chromogenic properties are epinephrine-like, encephalin is not epinephrine, tyramine, or vasopressin. It may be the Central Excitatory Agent of Page (181).

Calcium according to McNamara, Krop & McKay (182) potentiates the stimulating action of acetylcholine in the presence of atropine. This stimulating effect, blocked by nicotine, magnesium sulphate, Intocostrin, or dimethylpiperidine, may be restored by the addition of calcium.

Siegmund, Nash & Granger (183) examined cyclohexylisopropylamines and found that their pressor activity (intravenous) was much less than that of their phenyl analogues but that this difference was less evident when the drugs were given orally. Their pressor action *per os* was prolonged and their central nervous stimulating action relatively slight.

Lands *et al.* (184) studied *N*-alkyl substitution in norepineph-

[2] An extensive review of sympatholysis and sympatholytic drugs has recently been offered by Carl (237).

rine and found an increase in the sympathin action. Inhibitory effects are weak in hydroxytyramine derivatives containing no alcoholic hydroxyl. The same group (185) made extensive studies on the pressor activity of *N*-methyl-β-phenylisopropylamine and *N*-methyl-β-cyclohexylisopropylamine-hydrochloride. In a study of 2-amino-6-methyl-heptane (Oralator SKF), Fellows (186) finds it has one thousandth the pressor effect of epinephrine. The same author (187) has recently compared the pressor activity of seven sympathomimetic phenylpropylamines.

Lands and co-workers (188) add further to the study of sympathomimetics showing that substitutions which reduce the pressor effect or augment the depressor effects are widely mimetic of sympathin I.

Marrazzi & Marrazzi (189) discuss the relation of the chemical structure of sympathomimetics to sympathin E. They conclude that no known substance has the properties of sympathin E according to Cannon's definition which demands that it be purely excitatory.

Euler (190) further contributes to the discussion of the relationship between epinephrine, norepinephrine, and sympathin, suggesting for the first two the terms sympathin A and sympathin N.

Guest *et al.* (191) extracted from bovine plasma "vascularin," a euglobulin which lowers blood pressure and produces leukopenia with relative granulocytopenia. Vascularin stimulates rabbits' intestinal muscle and depresses turtles' hearts. It is nondialyzable, stable to reduction by cysteine or glutathione, and is unusually heat stable. It is not fibrinolysin.

Pentaquine produces its cardiovascular effects, say Richardson, Walker & Miller (192), by an impairment of the central portion of the sympathetic nervous system. Chen & Anderson (193) note that the antimalarial 4888 (Paludrine) lowers the blood pressure of anesthetized cats.

Hexaethyl tetraphosphate [Dayrit, Manry & Seevers (194)] inhibits cholinesterase and potentiates both pressor and depressor affects of acetylcholine.

According to Wills (195) organic nitrates (four tried) have little effect on veins but affect the arterial pressure gram for gram equally with sodium nitrite. Jablons (196) reports an adrenolytic substance in aglomerular fish kidney.

New sympatholytic drugs, dihydroergocornine and dihydro-

ergotamine (197, 198), and new adrenolytic compounds, naphthylmethylethyl-β-bromethylamine (SY-28) and β-(2-biphenyloxylethyl)-*n*-biethyl-β-chlorethylamine (S-30) have been investigated (199). Dihydroergocornine appears to be a pure sympatholytic acting predominantly on the medulla or hypothalamus.

Extensive writing has been done recently on the following drugs of interest to the cardiovascular physiologist: tetraethyl ammonium (200 to 206), dibenamine (207 to 210), benadryl (211 to 213), and rutin (214 to 216).

A study by Boyle *et al.* (217) of the effect of intravenous nicotine on the circulation of normal persons and patients with cardiovascular disease indicates large individual differences which were not related to the smoking habits or the cardiovascular status of the patient, except that some patients with coronary disease suffered from coronary insufficiency after the injection. Roth & Sheard (218) remark that the vasoconstriction from smoking is not prevented by the vasodilator effect of a moderate amount of alcohol or a good meal.

Vitamins.—Holman (219) showed that 4.0 mg. per kg. per day of mixed natural tocopherols (vitamin E) prevented the fatal generalized necrotizing arteritis which is produced in dogs by codliver oil (3 cc. per kg. per day).

Scurvy is early manifest in dilation and hyporeactivity of the minute contractile vessels of the guinea pig's mesentery [Lee & Lee (220)]. The petechial hemorrhages produced by trauma were almost all in the collecting venules. The capillaries were of normal diameter and no changes in the capillaries were observed.

Arterial Dynamics

There is no change in pulse wave velocity when the red cell count is lowered [Alexander & Webb (221)].

Ralston, Taylor & Elliott (222) report further studies on streamline flow in the arteries of the anesthetized cat. India ink injected into the arteries and directly observed through a glass segment inserted in the aorta or a large artery reveals that streamline flow is the rule. Radial movement of particles is observed only when a thrombus in the segment produces eddy currents. They confirmed Broemser's old observation (223) of retrograde movement of blood regularly in the cardiac cycle. Ink injected near the aortic orifice is not uniformly distributed to the renal and celiac

arteries. However, differences of distribution occurring when ink is injected into the ventricle are of low significance, the difference being such as would occur by chance six times in 100 observations. Remington *et al.* (238) studied 48 aortas and found an increase of capacity with age and hypertension, but the distensibility was variable and unpredictable.

General Observations

Revesz & Chase (224) adjusting teeth by orthodontic appliances find the trailing periodontal membrane is three to six times as vascular as that in the side toward which the tooth is moving.

Knisely *et al.* (225) review the work on "sludged blood," enumerating the experimental and pathological conditions in which it is found and illustrating some of the means by which it interferes with physiological function and produces structural damage. They speculate on the part played by cumulative minor sludge damage in the syndrome of senility.

Nervous mechanisms.—In chickens when the temperature rises the blood pressure rises also, and Rodbard & Tolpin (226) believe this protects the brain against any discrepancy between metabolism and blood supply. The mechanism is central. Acetylcholine circulation time [Rodbard & Fink (227)] in the chicken varies with body temperature. They note the depressor effect of acetylcholine occurs before the cardioinhibitory effect.

Electrical stimulation of the carotid sinus nerve in cats by Neil, Redwood & Schweitzer (228) produced the customary effects; but under chloralose the blood pressure rose. This pressor effect was not abolished by section of the vagus, the cervical sympathetic the contralateral carotid sinus nerve, the glossopharyngeal nerve, nor by adrenalectomy. It was, however, abolished by high spinal transection.

Using *in situ* perfusion of the innervated lung, Parin (229) studied pulmonary reflex control of the circulation. Increased pressure in the pulmonary artery always produced a fall in systemic arterial pressure and usually a fall in heart rate. These effects are clearly reflex and are mediated by the vagus nerve.

Methods.—Swann *et al.* (230) report that in dogs systolic arterial pressure is a more accurate criterion of the reversibility of anoxic death by resuscitation procedures than diastolic pressure, pulse pressure, breathing pattern, or duration of anoxia.

Rats' intestine quickly frozen, lyophiled, and cut in 10 μ sections showed the vasoconstriction and vasodilation characteristic of drugs administered just before freezing [Richins (231)].

McLain (232) compared three hematocrit methods quantitatively, showing that they all agreed to within 3 per cent but that higher precision could be obtained by careful selection of the appropriate method.

Marchal (233) uses the radiokymograph over the pulmonary parenchyma to study alterations of the flow in pulmonary arterioles, capillaries, and veins.

LITERATURE CITED

1. CRUICKSHANK, E. W. H., AND WHITFIELD, I. C., *J. Physiol. (London)*, **104,** 52–59 (1945)
2. BONNYCASTLE, D. D., *Am. J. Physiol.*, **151,** 504–8 (1947)
3. MILLER, A. T., JR., *Am. J. Physiol.*, **151,** 234–38 (1947)
4. MILLER, A. T., JR., *Am. J. Physiol.*, **151,** 229–33 (1947)
5. LAWSON, H. C., OVERBEY, D. T., MOORE, J. C., AND SHADLE, O. W., *Am. J. Physiol.*, **151,** 282–89 (1947)
6. OVERBEY, D. T., MOORE, J. C., SHADLE, O. W., AND LAWSON, H. C., *Am. J. Physiol.*, **151,** 290–96 (1947)
7. SHADLE, O. W., MOORE, J. C., AND LAWSON, H. C., *Federation Proc.*, **7,** 111 (1948)
8. MOORE, J. C., SHADLE, O. W., AND LAWSON, H. C., *Federation Proc.*, **7,** 82 (1948)
9. LAWSON, H. C., OVERBEY, D. T., SHADLE, O. W., AND MOORE, J. C., *Am. J. Physiol.*, **151,** 303–10 (1947)
10. LAWSON, H. C., SHADLE, O. W., MOORE, J. C., AND OVERBEY, D. T., *Am. J. Physiol.*, **151,** 297–302 (1947)
11. LEVEEN, H. H., AND FISHMAN, W. H., *Am. J. Physiol.*, **151,** 26–33 (1947)
12. GIBSON, J. G., AND EVANS, W. A., JR., *J. Clin. Invest.*, **16,** 301–16 (1937)
13. NIZET, A., *Quart. J. Exptl. Physiol.*, **34,** 123–28 (1948)
14. MORSE, M., CASSELS, D. E., SCHLUTZ, F. W., *Am. J. Physiol.*, **151,** 448–58 (1947)
15. NYLIN, G., *Am. Heart J.*, **34,** 174–79 (1947)
16. THOMPSON, S. A., AND ROCKEY, E. E., *Surg. Gynecol. Obstet.*, **84,** 1059–64 (1947)
17. SCHWARTZMAN, G., *et al.*, *Ann. N. Y. Acad. Sci.*, **49,** 483–660 (1948)
18. GREGERSEN, M. I., *Ann. N. Y. Acad. Sci.*, **49,** 542–48 (1948)
19. GREGERSEN, M. I., AND ROOT, W. S., *Am. J. Physiol.*, **148,** 98–123 (1947)
20. ROOT, W. S., WALCOTT, W. W., AND GREGERSEN, M. I., *Am. J. Physiol.*, **151,** 34–44 (1947)
21. ROOT, W. S., ALLISON, J. B., COLE, W. H., HOLMES, J. H., WALCOTT, W. W., AND GREGERSEN, M. I., *Am. J. Physiol.*, **149,** 52–63 (1947)
22. OVERMAN, R. R., AND WANG, S. C., *Am. J. Physiol.*, **148,** 289–95 (1947)
23. WANG, S. C., PAINTER, E. E., AND OVERMAN, R. R., *Am. J. Physiol.*, **148,** 69–76 (1947)
24. FOREMAN, R. C., *Proc. Soc. Exptl. Biol. Med.*, **65,** 28–33 (1947)
25. SHORR, E., ZWEIFACH, B. W., AND FURCHGOTT, R. F., *Ann. N. Y. Acad. Sci.*, **49,** 571–92 (1948)
26. SHORR, E., ZWEIFACH, B. W., FURCHGOTT, R. F., AND BAEZ, S., *Trans. Assoc. Am. Physicians*, **60,** 28 (1947)
27. CHAMBERS, R., AND ZWEIFACH, B. W., *Am. J. Physiol.*, **150,** 239–52 (1947)
28. WILHELMI, A. E., AND LONG, C. N. H., *Ann. N. Y. Acad. Sci.*, **49,** 605–21 (1948)
29. PHILLIPS, R. A., DOLE, V. P., HAMILTON, P. B., EMERSON, K., JR., ARCHIBALD, R. M., AND VAN SLYKE, D. D., *Am. J. Physiol.*, **145,** 314–36 (1946)
30. GIRALDI, E., PETERSON, L. W., AND COLE, W. H., *Proc. Soc. Exptl. Biol. Med.*, **66,** 277–78 (1947)

31. Cleghorn, R. A., *Can. J. Research*, [E]**25**, 86–99 (1947)
32. Henry, J., Goodman, J., Meehan, J., and Frankel, R., *J. Clin. Invest.*, **26**, 1119–29 (1947)
33. Little, J. M., Green, H. D., and Hawkins, J. E., Jr., *Am. J. Physiol.*, **151**, 554–63 (1947)
34. Bobb, J. R. R., and Green, H. D., *Am. J. Physiol.*, **150**, 700–4 (1947)
35. Lipton, E. L., Denison, A. B., and Green, H. D., *Am. J. Physiol.*, **150**, 693–96 (1947)
36. Goormaghtigh, N., *Am. J. Path.*, **23**, 513–24 (1947)
37. Corcoran, A. C., and Page, I. H., *J. Am. Med. Assoc.*, **134**, 436–41 (1947)
38. Harrison, H. E., Bunting, H., Ordway, N. K., and Albrink, W. S., *J. Exptl. Med.*, **86**, 339–56 (1947)
39. Alexander, R. S., and Webb, E. A., *Am. J. Physiol.*, **150**, 272–91 (1947)
40. Gibson, J. G., Seligman, A. M., Peacock, W. C., Fine, J., Aub, J. C., and Evans, R. D., *J. Clin. Invest.*, **26**, 126–44 (1947)
41. Root, W. S., Walcott, W. W., and Gregersen, M. I., *Am. J. Physiol.*, **151**, 34–44 (1947)
42. Harris, A. S., *Am. Heart. J.*, **35**, 895–909 (1948)
43. Hamilton, A. S., Parkins, W. M., and Waltzer, F., *Am. J. Physiol.*, **150** 641–53 (1947)
44. McCarthy, M. D., and Parkins, W. M., *Am. J. Physiol.*, **150**, 428–43 (1947)
45. Hamilton, P. B., Hiller, A., and Van Slyke, D. D., *J. Exptl. Med.*, **86**, 477–87 (1947)
46. Green, D. M., and Metheny, D., *Surg. Gynecol. Obstet.*, **84**, 1045–50 (1947)
47. Rocha e Silva, M., Scroggie, A. E., Fidlar, E., and Jaques, L. B., *Proc. Soc. Exptl. Biol. Med.*, **64**, 141–46 (1947)
48. Ferguson, J. H., *Ann. N. Y. Acad. Sci.*, **49**, 486–500 (1948)
49. Owren, P. A., *Acta Med. Scand.*, **128**, Suppl. 194, 1–327 (1947)
50. Quick, A. J., *Am. J. Physiol.*, **151**, 63–70 (1947)
51. Ware, A. G., Guest, M. M., and Seegers, W. H., *J. Biol. Chem.*, **169**, 231–32 (1947)
52. Munro, M. P., and Munro, F. L., *Am. J. Physiol.*, **150**, 409–14 (1947)
53. Ware, A. G., Guest, M. M., and Seegers, W. H., *Science*, **106**, 41–42 (1947)
54. Ware, A. G., Murphy, R. C., and Seegers, W. H., *Science*, **106**, 618–19 (1947)
55. Sykes, E. M., Jr., Seegers, W. H., and Ware, A. G., *Proc. Soc. Exptl. Biol. Med.*, **67**, 506–7 (1948)
56. Ruskin, A., and Decherd, G. M., Jr., *Am. J. Med. Sci.*, **213**, 337–41 (1947)
57. Wilburne, M., Schlichter, J. G., Grossman, M., and Cisneros, F., *Am. J. Physiol.*, **150**, 504–10 (1947)
58. Rodbard, S., and Fink, A., *Am. J. Physiol.*, **152**, 383–88 (1948)
59. Winsor, T., Adolph, W., Ralston, W., and Leiby, G. M., *Am. Heart J.*, **34**, 80–86 (1947)
60. Meneely, G. R., and Segaloff, A., *Am. J. Med. Sci.*, **214**, 176–79 (1947),
61. Myers, J. D., *J. Clin. Invest.*, **26**, 1130–37 (1947)
62. Ogden, E., and Tripp, E., *Am. J. Physiol.*, **153**, 190–96 (1948)
63. Munnell, E. W., and Taylor, H. C., Jr., *J. Clin. Invest.*, **26**, 952–56 (1947)

64. Bradley, S. E., Ingelfinger, F. J., Groff, A. E., and Bradley, G. P., *Proc. Soc. Exptl. Biol. Med.*, **67**, 206–7 (1948)
65. Bradley, S. E., and Conan, N. J., *J. Clin. Invest.*, **26**, 1175 (1947)
66. Wilkins, R. W., Culbertson, J. W., and Ingelfinger, F. J., *J. Clin. Invest.*, **26**, 1200 (1947)
67. Culbertson, J. W., Wilkins, R. W., Ingelfinger, F. J., and Bradley, S. E., *J. Clin. Invest.*, **26**, 1178 (1947)
68. Panzer, B. I., Baldwin, F. M., Ingall, F., and Heil, J. F., *Science*, **106**, 376 (1947)
69. Berry, M. R., Baldes, E. J., Essex, H. E., and Wakim, K. G., *J. Lab. Clin. Med.*, **33**, 101–17 (1948)
70. Fenn, W. O., Otis, A. B., Rahn, H., Chadwick, L. E., and Hegnauer, A. H., *Am. J. Physiol.*, **151**, 258–69 (1947)
71. Fenn, W. O., and Chadwick, L. E., *Am. J. Physiol.*, **151**, 270–75 (1947)
72. Gilliatt, R. W., *J. Physiol.* (*London*) **107**, 76–88 (1948)
73. Gilliatt, R. W., Guttmann, L., and Whitteridge, D., *J. Physiol.* (*London*) **107**, 67–75 (1948)
74. Hertzman, A. B., Crandall, W. C., and Jochim, K. E., *Am. J. Physiol.*, **150**, 122–32 (1947)
75. Halperin, M. H., Friedland, C. K., and Wilkins, R. W., *Am. Heart J.*, **35**, 221–37 (1948)
76. Wilkins, R. W., *N. Carolina Med. J.*, **8**, 297–300 (1947)
77. Scheinberg, P., Dennis, E. W., Robertson, R. L., and Stead, E. A., *Am. Heart J.*, **35**, 409–20 (1948)
78. Harpuder, K., Byer, J., and Stein, I. D., *Am. J. Physiol.*, **150**, 181–89 (1947)
79. Gubner, R., DiPalma, J. R., and Moore, E., *Am. J. Med., Sci.*, **213**, 46–52 (1947)
80. Roth, G. M., and Sheard, C., *Am. J. Physiol.*, **152**, 183–88 (1948)
81. Ogden, E., Clouse, C., and Murray, V., *Am. J. Physiol.* (In press)
82. Kemp, C. R., Tuttle, W. W., and Hines, H. M., *Am. J. Physiol.*, **150**, 705–11 (1947)
83. Hingson, R. A., and Southworth, J. L., *Military Surgeon*, **100**, 474–87 (1947)
84. Collins, V. J., Foster, W. L., and West, W. J., *New Engl. J. Med.*, **236**, 694–97 (1947)
85. Ferris, B. G., Jr., Forster, R. E., II, Pillion, E. L., and Christensen, W. R., *Am. J. Physiol.*, **150**, 304–14 (1947)
86. Barcroft, H., Bonnar, W. McK., and Edholm, O. G., *J. Physiol.* (*London*), **106**, 271–78 (1947)
87. Abramson, D. I., and Schumacker, H. B., Jr., *Am. Heart J.*, **33**, 500–7 (1947)
88. Johnson, C. A., *Arch. Phys. Med.*, **28**, 351–57 (1947)
89. Lange, K., Weiner, D., and Boyd, L. J., *Am. Heart J.*, **35**, 238–47 (1948)
90. Brown, E., Wise, C. S., and Wheeler, E. O., *J. Clin. Invest.*, **26**, 1031–42 (1947)
91. Herlihy, W. F., *Med. J. Australia*, **I**, 661–71 (1947)
92. Bradley, S. E., and Bradley, G. P., *J. Clin. Invest.*, **26**, 1010–22 (1947)
93. Booker, W. M., French, D. M., and Molano, P. A., *Am. J. Physiol.*, **149**, 292–98 (1947)

94. ALTSCHULE, M. D., FREEDBERG, A. S., AND MCMANUS, M. J., *Arch. Internal Med.*, **80**, 491–95 (1947)
95. MACKAY, I. F. S., *J. Physiol. (London)*, **106**, 113–18 (1947)
96. SLOCUM, H. C., HOEFLICH, E. A., AND ALLEN, C. R., *Surg. Gynecol. Obstet.*, **84**, 1051–58 (1947)
97. SLOCUM, H. C., O'NEAL, K. C., AND ALLEN, C. R., *Surg. Gynecol. Obstet.*, **86**, 729–34 (1948)
98. RUSHMER, R. F., BECKMAN, E. L., AND LEE, D., *Am. J. Physiol.*, **151**, 355–65 (1947)
99. BRITTON, S. W., PERTZOFF, V. A., FRENCH, C. R., AND KLINE, R. F., *Am. J. Physiol.*, **150**, 7–26 (1947)
100. VAN MIDDLESWORTH, L., AND KLINE, R. F., *Am. J. Physiol.*, **152**, 22–26 (1948)
101. TAYLOR, H. L., HENSCHEL, A., AND KEYS, A., *Am. J. Physiol.*, **152**, 141–49 (1948)
102. REYNOLDS, S. R. M., *Am. J. Physiol.*, **148**, 77–85 (1947)
103. REYNOLDS, S. R. M., *Am. J. Obstet. Gynecol.*, **53**, 221–25 (1947)
104. REYNOLDS, S. R. M., *Endocrinology*, **40**, 381–87 (1947)
105. REYNOLDS, S. R. M., *Endocrinology*, **40**, 388–94 (1947)
106. BROWN, E., SAMPSON, J. J., WHEELER, E. O., GUNDELFINGER, B. F., AND GIANSIRACUSA, J. E., *Am. Heart J.*, **34**, 311–33 (1947)
107. PRINZMETAL, M., ORNITZ, E. M., JR., SIMKIN, B., AND BERGMAN, H. C., *Am. J. Physiol.*, **152**, 48–52 (1948)
108. MONTGOMERY, L. H., AND WARD, J. W., *Rev. Sci. Instruments*, **18**, 289–93 (1947)
109. LILLY, J. C., LEGALLAIS, V., AND CHERRY, R., *J. Applied Phys.*, **18**, 613–28 (1947)
110. KERSTEN, H., BROSENE, W. G., JR., ABLONDI, F., AND SUBBAROW, Y., *J. Lab. Clin. Med.*, **32**, 1090–98 (1947)
111. ABLONDI, F., SUBBAROW, Y., LIPCHUCK, L., AND PERSONEUS, G., *J. Lab. Clin. Med.*, **32**, 1099–1106 (1947)
112. CHITTUM, J. R., HILL, H. C., AND GRIMSON, K. S., *Proc. Soc. Exptl. Biol. Med.*, **66**, 486–88 (1947)
113. HELLEMS, H. K., DEXTER, L., AND HAYNES, F. W., *J. Clin. Invest.*, **26**, 1184 (1947)
114. BING, R. J., VANDAM, L. D., GRÉGOIRE, F., HANDELSMAN, J. C., GOODALE, W. T., AND ECKENHOFF, J. E., *Proc. Soc. Exptl. Biol. Med.*, **66**, 239–40 (1947)
115. BOYNTON, R. E., AND TODD, R. L., *Arch. Internal Med.*, **80**, 454–62 (1947)
116. CURRENS, J. H., *Am. Heart J.*, **35**, 646–54 (1948)
117. SCHAPOSNIK, F., *Rev. clin. espan.*, **24**, 26–30 (1947)
118. OGDEN, E., *Bull. N. Y. Acad. Med.*, **23**, 643–60 (1947)
119. HAYNES, F. W., AND DEXTER, L., *Am. J. Physiol.*, **150**, 190–97 (1947)
120. OGDEN, E., COLLINGS, W. D., AND SAPIRSTEIN, L. A., *Experimental Hypertension*, Special Pub. N. Y. Acad. Sci., **3**, 153–67 (1946)
121. MYLON, E., AND HELLER, J. H., *Proc. Soc. Exptl. Biol. Med.*, **67**, 62–67 (1948)
122. TRIPP, E., AND OGDEN, E., *Federation Proc.*, **6**, 216–17 (1947)
123. PAGE, I. H., *Experimental Hypertension*, Special Pub. N. Y. Acad. Sci., **3**, 77–98 (1946)

124. TRAUTMAN, W. J., JR., DAVIS, W. D., AND FINDLEY, T., *J. Lab. Clin. Med.*, **32**, 1482–85 (1947)
125. HELMER, O. M., AND SHIPLEY, R. E., *Am. J. Physiol.*, **150**, 353–57 (1947)
126. SCHROEDER, H. A., *Pressor Materials in Blood of Human Hypertensives* (Presented at Josiah Macy, Jr. Foundation Conf., New York, N. Y., January 9, 1948
127. MYLON, E., LUND, M., AND HELLER, J. H., *Am. J. Physiol.*, **152**, 397–406 (1948)
128. SHIPLEY, R. E., AND TILDEN, J. H., *Proc. Soc. Exptl. Biol. Med.*, **64**, 453–55 (1947)
129. GOLLAN, F., RICHARDSON, E., AND GOLDBLATT, H., *J. Exptl. Med.*, **87**, 29–39 (1948)
130. LEWIS, L. A., AND PAGE, I. H., *J. Exptl. Med.*, **86**, 185–92 (1947)
131. FORSTER, R. P., AND MAES, J. P., *Am. J. Physiol.*, **150**, 534–40 (1947)
132. GRIMSON, K. S., BOUCKAERT, J. J., AND HEYMANS, C., *Proc. Soc. Exptl. Biol. Med.*, **42**, 225–26 (1939)
133. TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., AND PRICHARD, M. M. L., *Studies of the Renal Circulation*, 187 pp. (Charles C Thomas, Springfield, Ill., 1947)
134. KOTTKE, F. J., KUBICEK, W. G., AND LAKER, D. J., *Arch. Phys. Med.*, **28**, 146–53 (1947)
135. FRIEDMAN, S. M., AND FRIEDMAN, C. L., *Can. Med. Assoc. J.*, **56**, 655–58 (1947)
136. FRIEDMAN, S. M., POLLEY, J. R., AND FRIEDMAN, C. L., *J. Exptl. Med.*, **87**, 329–38 (1948)
137. PERERA, G. A., AND BLOOD, D. W., *Ann. Internal Med.*, **27**, 401–4 (1947)
138. PRADO, J. L., DONTIGNY, P., AND SELYE, H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 446–48 (1947)
139. SOBIN, S. S., AND LANDIS, E. M., *Am. J. Physiol.*, **148**, 557–62 (1947)
140. ABRAMS, M., AND SOBIN, S., *Proc. Soc. Exptl. Biol. Med.*, **64**, 412–16 (1947)
141. ZBINDEN, F., *Helv. Physiol. et Pharmacol. Acta*, **4**, 513 (1946)
142. GROLLMAN, A., *Am. J. Physiol.*, **151**, 373–79 (1947)
143. WASTL, H., *Arch. intern. pharmacodynamie*, **74**, 1–8 (1947)
144. COOKE, W. T., AND BARCLAY, J. A., *Brit. Heart J.*, **8**, 237 (1946)
145. POPPEN, J. L., *Surg. Gynecol. Obstet.*, **84**, 1117–23 (1947)
146. DETAKATS, G., AND FOWLER, E. F., *Surgery*, **21**, 773–99 (1947)
147. FREIS, E. D., AND SMITHWICK, R. H., *Am. J. Med. Sci.*, **214**, 363–67 (1947)
148. LANDOWNE, M., AND ALVING, A. S., *Proc. Soc. Exptl. Biol. Med.*, **67**, 115–18 (1948)
149. BIRCHALL, R., TAYLOR, R. D., LOWENSTEIN, B. E., AND PAGE, I. H., *Am. J. Med. Sci.*, **213**, 572–78 (1947)
150. OSTER, J., *Acta Med. Scand.*, **128**, 42–50 (1947)
151. HARDWICK, C., AND BADENOCH, A. W., *Brit. Med. J*, **1**, 293–96 (1947)
152. HAYNES, F. W., DEXTER, L., AND SEIBEL, R. E., *Am. J. Physiol.*, **150**, 198–201 (1947)
153. KRIEGER, V. I., AND WEIDEN, S., *Med. J. Australia*, **I**, 417–23 (1947)
154. TALSO, P. J., CROSLEY, A. P., AND CLARKE, R. W., *J. Lab. Clin. Med.*, **33**, 430–34 (1948)

155. Bradley, S. E., Chasis, H., Goldring, W., and Smith, H. W., *J. Clin. Invest.*, **24**, 749–58 (1945)
156. Rosenkrantz, J. A., and Marshall, C., *Arch. Int. Med.*, **80**, 81–88 (1947)
157. Selye, F., *J. Clin. Invest.*, **26**, 1197 (1947)
158. Taylor, R. D., Corcoran, A. C., and Page, I. H., *Am. J. Med. Sci.*, **213**, 475–76 (1947)
159. Hinchey, J. J., Hines, E. A., Jr., and Ghormley, R. K., *Proc. Staff Meetings Mayo Clinic*, **22**, 275–76 (1947)
160. Heinbecker, P., *Surgery*, **23**, 618–38 (1948)
161. Moreton, J. R., *Science*, **107**, 371–73 (1948)
162. Gordon, I., *Arch. Path.*, **44**, 247–60 (1947)
163. Boas, E. P., Parets, A. D., and Adlersberg, D., *Am. Heart J.*, **35**, 611–22 (1948)
164. Kellner, A., Correll, J. W., and Ladd, A. T., *Proc. Soc. Exptl. Biol. Med.*, **67**, 25–27 (1948)
165. Steiner, A., and Kendall, F. E., *Arch. Path.*, **42**, 433–44 (1946)
166. Blumenthal, L. S., *Arch. Path.*, **44**, 372–79 (1947)
167. Buck, R. C., *Univ. Western Ontario Med. J.*, **17**, 1–11 (1947)
168. De la Barreda, P., Diaz, C. J., and de Molina, A. F., *Rev. españ. cardiol.*, **1**, 1 (1947)
169. Goldman, M. L., and Schroeder, H. A., *Science*, **107**, 272–73 (1948)
170. Perera, G. A., *Proc. Soc. Exptl. Biol. Med.*, **68**, 48–50 (1948)
171. Kochakian, C. D., and Dontigny, P., *Proc. Soc. Exptl. Biol. Med.*, **67**, 61–62 (1948)
172. Selye, H., *Rev. can. biol.*, **6**, 799–800 (1947)
173. Mylon, E., Horton, F. H., and Levy, R. P., *Proc. Soc. Exptl. Biol. Med.*, **66**, 375–77 (1947)
174. Mylon, E., and Heller, J. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 319–21 (1947)
175. Mylon, E., Horton, F. H., and Levy, R. P., *Proc. Soc. Exptl. Biol. Med.*, **66**, 378–80 (1947)
176. Edman, P., *Arkiv. Kemi Mineral. Geol.*, [E] **22**, 1–50 (1945)
177. Bülbring, E., Burn, J. H., and de Elío, F. J., *J. Physiol. (London)*, **107**, 222–32 (1948)
178. Barclay, J. A., Cooke, W. T., and Kenney, R. A., *Am. J. Physiol.*, **151**, 621–25 (1947)
179. McDowall, R. J. S., *J. Physiol. (London)*, **106**, 1–7 (1947)
180. Raab, W., *Am. J. Physiol.*, **152**, 324–39 (1948)
181. Page, I. H., *Am. J. Physiol.*, **120**, 392–400 (1937)
182. McNamara, B., Krop, S., and McKay, E. A., *J. Pharmacol. Exptl. Therap.*, **92**, 153–61 (1948)
183. Siegmund, O. H., Nash, V. L., and Granger, H. R., *J. Pharmacol. Exptl. Therap.*, **92**, 207–13 (1948)
184. Lands, A. M., Nash, V. L., Dertinger, B. L., Granger, H. R., and McCarthy, H. M., *J. Pharmacol. Exptl. Therap.*, **92**, 369–80 (1948)
185. Lands, A. M., Nash, V. L., Granger, H. R., and Dertinger, B. L., *J. Pharmacol. Exptl. Therap.*, **89**, 382–85 (1947)
186. Fellows, E. J., *J. Pharmacol. Exptl. Therap.*, **90**, 351–58 (1947)

187. FELLOWS, E. J., *Proc. Soc. Exptl. Biol. Med.*, **65**, 261–65 (1947)
188. LANDS, A. M., RICKARDS, E. E., NASH, V. L., AND HOOPER, K. Z., *J. Pharmacol. Exptl. Therap.*, **89**, 297–305 (1947)
189. MARRAZZI, A. S., AND MARRAZZI, R. N., *Science*, **106**, 520–21 (1947)
190. EULER, U. S. v., *Science*, **107**, 422 (1948)
191. GUEST, M. M., MURPHY, R. C., BODNAR, S. R., WARE, A. G., AND SEEGERS, W. H., *Am. J. Physiol.*, **150**, 471–79 (1947)
192. RICHARDSON, A. P., WALKER, H. A., AND MILLER, B. S., *Proc. Soc. Exptl. Biol. Med.*, **65**, 258–261 (1947)
193. CHEN, K. K., AND ANDERSON, R. C., *J. Pharmacol. Exptl. Therap.*, **91**, 157–60 (1947)
194. DAYRIT, C., MANRY, C. H., AND SEEVERS, M. H., *J. Pharmacol. Exptl. Therap.*, **92**, 173–86 (1948)
195. WILLS, J. H., *Proc. Soc. Exptl. Biol. Med.*, **65**, 161–63 (1947)
196. JABLONS, B., *Nature*, **161**, 100–1 (1948)
197. BLUNTSCHLI, H. J., AND GOETZ, R. H., *Am. Heart J.*, **35**, 873–94 (1948)
198. BLUNTSCHLI, H. J., AND GOETZ, R. H., *S. African Med. J.*, **21**, 382–401 (1947)
199. DE VLEESCHHOUWER, G. R., *Proc. Soc. Exptl. Biol. Med.*, **67**, 298–99 (1948)
200. COOPER, F. W., JR., ROBERTSON, R. L., AND DENNIS, E. W., *Surgery*, **22**, 740–45 (1947)
201. CORCORAN, A. C., AND PAGE, I. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 148–51 (1947)
202. BIRCHALL, R., TAYLOR, R. D., LOWENSTEIN, B. E., AND PAGE, I. H., *Am. J. Med. Sci.*, **213**, 572–78 (1947)
203. GRUHZIT, O. M., FISKEN, R. A., AND COOPER, B. J., *J. Pharmacol. Exptl. Therap.*, **92**, 103–7 (1948)
204. LYONS, R. H., MOE, G. K., NELIGH, R. B., HOOBLER, S. W., CAMPBELL, K. N., BERRY, R. L., AND RENNICK, B. R., *Am. J. Med. Sci.*, **213**, 315–23 (1947)
205. PAGE, I. H., AND TAYLOR, R. D., *J. Am. Med. Assoc.*, **135**, 348–49 (1947)
206. PAGE, I. H., AND TAYLOR, R. D., *Science*, **105**, 622 (1947)
207. YOUMANS, W. B., AND RANKIN, V. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 241–44 (1947)
208. DE VLEESCHHOUWER, G. R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 151–52 (1947)
209. SIMEONE, F. A., AND SARNOFF, S. J., *Surgery*, **22**, 391–401 (1947)
210. WILBURNE, M., KATZ, L. N., RODBARD, S., AND SURTSHIN, A., *J. Pharmacol. Exptl. Therap.*, **90**, 215–23 (1947)
211. CHEN, G., ENSOR, C. R., AND CLARKE, I. G., *J. Pharmacol. Exptl. Therap.*, **92**, 90–97 (1948)
212. GRUHZIT, O. M., AND FISKEN, R. A., *J. Pharmacol. Exptl. Therap.*, **89**, 227–33 (1947)
213. WINDER, C. V., AND THOMAS, R. W., *J. Pharmacol. Exptl. Therap.*, **91**, 1–14 (1947)
214. AMBROSE, A. M., AND DEEDS, F., *J. Pharmacol. Exptl. Therap.*, **90**, 359–63 (1947)
215. WILSON, R. H., MORTAROTTI, T. G., AND DEEDS, F., *J. Pharmacol. Exptl. Therap.*, **90**, 120–27 (1947)

216. WILSON, R. H., MORTAROTTI, T. G., AND DOXTADER, E. K., *Proc. Soc. Exptl. Biol. Med.*, **64**, 324–27 (1947)
217. BOYLE, M. N., WÉGRIA, R., CATHCART, R. T., NICKERSON, J. L., AND LEVY, R. L., *Am. Heart J.*., **34**, 65–79 (1947)
218. ROTH, G. M., AND SHEARD, C., *Am. Heart J.*, **33**, 654–62 (1947)
219. HOLMAN, R. L., *Proc. Soc. Exptl. Biol. Med.*, **66**, 307–9 (1947)
220. LEE, R. E., AND LEE, N. Z., *Am. J. Physiol.*, **149**, 465–75 (1947)
221. ALEXANDER, R. S., AND WEBB, E. A., *Am. J. Physiol.*, **149**, 316–18 (1947)
222. RALSTON, H. J., TAYLOR, A. N., AND ELLIOTT, H. W., *Am. J. Physiol.*, **150**, 52–57 (1947)
223. BROEMSER, P., *Z. Biol.*, **88**, 264–76 (1928)
224. REVESZ, J., AND CHASE, S. W., *J. Dental Research*, **26**, 143–50 (1947)
225. KNISELY, M. H., BLOCH, E. H., ELIOT, T. S., AND WARNER, L., *Science*, **106**, 431–40 (1947)
226. RODBARD, S., AND TOLPIN, M., *Am. J. Physiol.*, **151**, 509–15 (1947)
227. RODBARD, S., AND FINK, A., *Am. J. Physiol.*, **152**, 383–88 (1948)
228. NEIL, E., REDWOOD, C. R. M., AND SCHWEITZER, A., *J. Physiol.* (*London*), **107**, 8P–9P (1948)
229. PARIN, V. V., *Am. J. Med. Sci.*, **214**, 167–75 (1947)
230. SWANN, H. G., BRUCER, M., MOORE, C., AND VEZIAN, B. L., *Memorandum Rept. MCREXD-696-79 G*, Air Materiel Command, U. S. Air Force (1948)
231. RICHINS, C. A., *Science*, **107**, 25 (1948)
232. MCLAIN, P. L., *Science*, **106**, 275–76 (1947)
233. MARCHAL, M., *Arch. maladies coeur et vaisseaux*, **39**, 345–59 (1946)
234. MOORE, J. C., SHADLE, O. W., AND LAWSON, H. C., *Am. J. Physiol.*, **153**, 322–29 (1948)
235. WU, H. C., AND VISSCHER, M. B., *Am. J. Physiol.*, **153**, 330–35 (1948)
236. SHIPLEY, R. E., AND HELMER, O. M., *Am. J. Physiol.*, **153**, 341–47 (1948)
237. CARL, G. P., GPC/HWT Literature Research Dept., Smith, Kline & French Laboratories (1948)
238. REMINGTON, J. W., NOBACK, C. R., HAMILTON, W. F., AND GOLD, J. J., *Am. J. Physiol.*, **153**, 298–308 (1948)

RESPIRATION

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The review is concerned with external or "somatic" respiration, particularly lung breathing. Owing to reduced space allotted and the increasing number of publications on the subject, the general effects of respiratory and other gases on the body tissues and organs had to be omitted. Thus neither anoxia nor mechanical effects of barometric pressure are included, and clinical applications are only briefly mentioned. The period covered extends from July, 1947 to April, 1948; some earlier papers from continental European journals not reviewed in last year's article (1) were also taken into account.

Herlitzka (2), on the occasion of the centenary of Angelo Mosso's birth (May 30, 1946), recalls the work of the Italian pioneer in respiratory physiology. Recent literature on respiration in relation to allergy is reviewed by Brown (3). A valuable account of respiratory problems in aviation physiology is given by Malmé-jac in his monograph (4).

Lungs and Respiratory Tract—Mechanics of Air Breathing

Policard studied the histophysiological structure of the peripheral zone of the primary lung lobule (5) and emphasizes the difficulty in distinguishing broncho-epithelial from alveolar wall cells (6). The distensibility of lung tissue, as determined either on the isolated organ or *in situ* in the open-chest dog, was found to decrease in a reversible manner with vascular congestion [Mack *et al.* (7)]. Loss of distensibility of lung tissue is considered by Heyer *et al.* (8) as a primary factor in altering dynamics of respiration in pulmonary congestion induced experimentally on dogs by rapid venous infusion. Lung lobes deprived of pulmonary artery flow diminish in expansibility, but not in weight and collapsed volume [Lindskog & Gilman (9)]. Campbell & Harvey (10) showed that the reduction in vital capacity coincident with recumbency is due to reflux of venous blood from the extremities rather than from trunk and head. Vital capacity of old people was investigated by Grailly & Marchal (11). Veen (12) found only resid-

ual air in lungs of drowned animals. Caruso & Stassi (13) consider both increased air and water content as responsible for the hypervolume of lungs after drowning. Respiratory efficiency in patients with pneumothorax was studied by Donno (14).

Wiggers *et al.* (15) recorded with an improved air pocket technique intrathoracic pressures from different regions of the chest of anesthetized dogs. In human subjects, pulmonary function was estimated from various respiratory data, in relation to body posture [Mitolo (16)], as well as in twelve different operating positions [Sokalchuk *et al.* (17)]. In order to determine lung expansibility and air-flow resistance, pressure-volume diagrams of the respiratory act have been recorded by Rowinski & Talenti (18) on decerebrate dogs. Otis & Proctor (19) measured alveolar pressure and simultaneous rate of flow of inspired air in man. Data obtained by Specht (20) on the velocity pattern of the breath seem to indicate that at low barometric pressures, breathing efficiency is altered mechanically by reduced density of the respired air. Gierke (21) demonstrated the turbulence occurring periodically in the blast of air passing between the lips while whistling. Sloan *et al.* (22) stated that nebulized solutions of several substances inhaled by eupneic breathing mice, rats, rabbits, and dogs do not reach the alveoli, and even in bronchioles and bronchi small amounts only were found. A method of determining the depth of penetration of aerosols within the respiratory tract of man by the use of radioactive sodium has been developed by Talbot *et al.* (23). Policard (24) injected Tyrode suspensions of silicon into the bronchial tree of guinea pigs and found the finest particles down to the alveoli.

In dogs and guinea pigs the bronchomotor activity as controlled by vagal parasympathetic innervation and by hormones and drugs has been investigated by Binet & Burstein (25). The bronchodilator action of epinephrine and structurally related compounds, as well as of synthetic antihistamines, has been studied by Halpern *et al.* (26), Siegmund *et al.* (27), and Lerman & Goldfeder (28). Curare, when given to human subjects in appropriate doses, may relax the bronchial musculature as shown by Benda *et al.* (29) in a few cases of bronchoscopic examination. Castillo & De Beer (30, 31) developed a guinea pig trachea preparation ("Tracheal chain") to be used as an anaphylactic test object. Intravenously injected di-isopropylfluorophosphate produced

bronchospasm in dogs when given in relatively large doses [Heymans & Jacob (32)]. Bronchoconstrictor action of curarizing drugs was also reported by Landmesser (33). Minet *et al.* (34) recommend administration of aerosols of bronchoconstrictor and bronchodilator substances and examination of their effect on the pneumogram as a functional respiratory test in man. Barach & Garthwaite (35) considered therapy of bronchial asthma from the physiological point of view. Wyss (36) measured air flow velocity during sudden expiration on asthmatic children, thus determining expiratory resistance of bronchial passage.

Pulmonary Circulation

Visscher (37) determined the changes of pulmonary vascular bed volume occurring with variations of intrathoracic pressure. The isolated dog lung was placed in a glass chamber together with the whole volume recording system and exposed to simulated intrathoracic pressures. Blood capacity was found maximum for −4 cm. water and diminishing at more negative pressures. It thus decreases during normal inspiration and increases during passive expiration. Bruner & Schmidt (38) performed on anesthetized dogs an extensive study of the bronchial artery blood supply, of its intra- and extrapulmonic vascular connections and their relation to pulmonary and systemic circulation. Bronchial venous circulation was examined histologically by De Busscher (39). Arteriovenous anastomoses of the lung were studied with a glass sphere passage technique by Prinzmetal *et al.* (40).

An indirect method for determining pulmonary capillary blood flow by means of a carbon dioxide equilibration technique has been developed by Bing *et al.* (41, 42, 43) and Vandam *et al.* (44). Compared with the direct right heart catheterization method, it allows collateral circulation to the lungs to be calculated; but differences up to 30 per cent are found in subjects having no known intracardiac shunts [Gray *et al.* (45)]. In human cases of interatrial septal defect pulmonary blood flow is increased by back flow from left to right atrium as concluded by Cournand *et al.* (46) from intracardiac pressure measurements showing elevated pressure in the right ventricle and a mean pressure higher in the left than in the right atrium.

In man, where rapid changes in pulmonary arterial pressure are considered by Cournand (47) as being chiefly caused by varia-

tion in blood flow and not by vasomotor regulation, the marked drop of pulmonary vascular resistance as found by Riley *et al.* (48) during exercise seems to depend on inspiratory expansion of the vascular bed rather than on active vasodilatation. Patients with chronic pulmonary disease have lost such expansibility of lungs and pulmonary vascular bed. Motley *et al.* (49) have shown that pulmonary arterial hypertension is rapidly induced by low (10 per cent) oxygen breathing, even under slightly decreased cardiac output. Pulmonary vascular resistance is therefore increased during alveolar anoxia, either by stasis in the smaller pulmonary vessels, as suggested by Drinker [cf. (49)], or by arteriolar constriction due to local lack of oxygen [Euler & Liljestrand (50), Heemstra (115)]. The latter view is further supported by Logaras (51), who found on cats and dogs that anoxic increase of pulmonary arterial pressure is not affected by ergotamine or atropine, nor related drugs; but ergotamine seems by itself to constrict pulmonary arterioles. Carbon dioxide has only a slight constrictor effect, which is abolished by ergotamine. Logaras also stated that increased respiratory resistance during inspiration or expiration produces a rise in pulmonary arterial pressure. Increased vascular resistance to lung lobe perfusion has been noted by Burstein (52) to occur with intratracheal pressure rise, i.e., with lung distension. Pulmonary arterial pressure has been studied in the chicken by Brown & Rodbard (53), its maintenance after severe right ventricular damage in dogs, by Bakos (54). Restricted pulmonary emboli may cause a marked rise of pulmonary arterial pressure, with ensuing circulatory failure, as shown experimentally by Smith & Hara (55). This may explain the treatment of pulmonary embolism by stellate block [Bageant & Raper (56)]. Systemic hypotension originating reflexly from pulmonary arterial pressure rise was studied by Parin (57) on cats. Further clinical inferences concerning pulmonary arterial pressure have been reported by several authors (58 to 62).

Pulmonary capillary circulation has been investigated by Vogel (63) with a microcinematographic method. The velocity of intravenously introduced India ink particles measured in capillaries near the lung surface of the cat was found to average between 1 and 2 mm. per sec. Thus red cells would remain in contact with the alveolar wall for less than 0.1 sec., which does not seem suffi-

cient for oxygen uptake following known physicochemical laws. Dexter *et al.* (64), by venous catheterization on man, obtained "capillary" blood from the lung through pulmonary artery branches obstructed by the catheter. Data pertaining to lymph formation and drainage in the lungs, as well as to fluid exchange and pulmonary edema, have been presented in various articles (65 to 73).

In studying vasomotor reactions of the lesser circulation by means of a pulmonary lobe perfusion technique, Burstein (52) recorded vasoconstriction from sympathetic stimulation or epinephrine. On the perfused living animal preparation (dog) Daly *et al.* (74, 75) obtained pulmonary vasoconstriction and sometimes vasodilation when stimulating the upper sympathetic chain including stellate and middle cervical ganglions. Fibres involved in both reactions are stated to be postganglionic and of the adrenergic type. On the frog's perfused lung, Brecht (76) observed vasoconstriction following single shock stimulation of the vagosympathetic nerve, as well as with injection of acetylcholine.

Pressure Breathing

In the animal experiments of Logaras (51), pulmonary arterial pressure was not affected when intrapulmonic pressure was kept at a higher level throughout the respiratory cycle. In anesthetized or decerebrate dogs, Elwell & Bean (77) found an enhancement of neuromuscular response to motor nerve stimulation, which is gradual at onset and persists as long as positive pressure breathing is maintained. It seems to be due to diminished blood flow through the limb and resulting humoral changes. A simple device for pressure breathing of experimental animals has been described by Holldack (78).

In the human subject, breathing against continuous pressures from 30 to 50 mm. Hg for periods of fifteen to thirty minutes, considerable hemoconcentration (e.g., 4 to 10 volume per cent) is induced by the rise of mean venous pressure and ensuing disturbance of fluid equilibrium, as reported by Henry *et al.* (79). On account of distension of the venous reservoirs, continuous pressure breathing for thirty minutes at 50 mm. Hg may entail a total loss of circulating blood volume amounting to as much as 20 per cent [Jacobs *et al.* (80)]. This confirms earlier war contract work of Fenn *et al.* (81), who by using a combined teeter-board and plethysmographic method, showed that, when breathing

against 30 cm. water, about half of the blood contained in the lungs, i.e., almost 10 per cent of the total blood volume, is displaced into the legs and abdomen. With this passive increase of leg volume avoided by applying a suitably inflated pneumatic cuff above the plethysmograph, pressure breathing causes a decrease in leg volume due to vasoconstriction. Peripheral vasoconstriction during positive pressure breathing has likewise been demonstrated by Fenn & Chadwick (82) with a finger plethysmograph technique, showing a decrease of pulse volume and blood flow. De Lalla (83), measuring the skin temperature, presented evidence for the reflex nature of the peripheral vasomotor effect, which occurs also in negative pressure breathing, and even better when expansion of the chest in positive pressure breathing is prevented by a pneumatic vest, as well as after single deep and rapid inspiration or expiration. Independently from pressure breathing studies, inspiratory vasoconstriction has been investigated in normal subjects by Gilliatt (84) and in paraplegic patients by Gilliatt *et al.* (85) and was found to be a purely spinal reflex. Some relation to galvanic skin reflex may be suggested. Effects of continuous pressure breathing on kidney function and intracranial pressure have been reported by Drury *et al.* (86) and Adler (87, 88), respectively. Otis *et al.* (89) observed similar respiratory and cardiac changes, both from positive pressure breathing and tilting of the body. Alveolar carbon dioxide tension is lowered, whereas alveolar oxygen pressure, breathing frequency, tidal volume, and heart rate are increased. Marchal (90) recorded x-ray density of lung parenchyma in human subjects and obtained vascular pulsations synchronous with the heart beat, which can be suppressed by breathing against positive pressures. The method may provide some correlate of pulmonary vascular pressure.

Intermittent positive pressure breathing has been studied by Cournand *et al.* (91) with regard to its decreasing effect on cardiac output. This largely depends upon the shape of the mask pressure curve. No decrease occurred with gradually increasing pressure during inspiration and sudden drop early during expiration, expiratory time being somewhat longer than inspiratory time. The clinical requirements to be met by intermittent positive pressure breathing in its use as a therapeutic procedure have been discussed in detail by Motley *et al.* (92). As a method of increasing altitude tolerance, the intermittent type of pressure breathing was not

found to result in as good a performance as the continuous type, the former involving the danger of hyperventilation with alkalosis [Eckman *et al.* (93)]. Circulatory depression may occur during controlled respiration as used in clinical anesthesia [Papper & Reaves (94)]. Boche *et al.* (95) applied oxygen by intermittent positive pressure breathing of the inspiratory as well as of the expiratory types to phosgene-gassed dogs suffering from pulmonary edema; but no reduction of mortality or improvement was noted. Anesthetized dogs breathing against inspiratory or expiratory airway resistances of 20 cm. water develop pulmonary edema, congestion, and hemorrhage within six to eight hours; but there is no increase in tendency to lung edema after bilateral vagotomy [Zinberg *et al.* (96)]. Essentially the same results were attained by Sussman *et al.* (97) on guinea pigs. Jacobs (98, 99) studied the effects of breathing with the Burns pneumatic balance resuscitator on pulmonary ventilation and arterial blood carbon dioxide and pH.

Respiratory Gas Exchange

By measuring continuously and simultaneously volume flow and nitrogen content of gas expired following inhalation of 99.6 per cent oxygen, Fowler (100) found on thirty normal human males an average respiratory dead space of 155 ml. and an average expired volume required to wash out the dead space of 317 ml. The method allows the determination of the degree of uniformity of gas mixing within the lungs and respiratory passages. Boeri & Vacca (101) developed the hydrogen method of dead space determination in man. Using an improved technique of automatic collection of alveolar air, Lambie & Morrissey (102) confirmed Haldane & Priestley's observation that physiological dead space is smaller for carbon dioxide than it is for oxygen. Rahn & Otis (103), by continuous sampling of alveolar air and minute to minute recording of its gas composition up to high simulated altitudes, found higher oxygen and lower carbon dioxide values than with Haldane's method. But differences lessen as altitude increases. Extensive data are presented concerning respiratory behaviour of trained subjects under varying experimental conditions. Otis *et al.* (104) compared alveolar gas changes during breath-holding at low and high inspired air oxygen tensions and studied the conditions determining the breaking point. Sampling of alveolar air by bronchial catheterization has been studied on dogs by Cordier &

Cordier (105) and on patients by Birath (106). Stacy *et al.* (107) applied the mass spectrometer to rapid, continuous, and simultaneous analysis of oxygen, carbon dioxide, and nitrogen in respiratory gases. They did not find an oxygen trough in alveolar air expulsions. Blinn & Noell (108) developed a method for continuous recording of alveolar carbon dioxide to be used in controlling a hyperventilation test. Some exchange of carbon dioxide and oxygen has been reported by Galdston & Horwitz (109) to take place across the pharyngeal mucosa. Buccopharyngeal respiration has also been studied by Oglialoro (110) on teleosts.

The view held by Sturm (111) that capillary permeability in either direction is rather due to intercellular plasma flow than to diffusion through endothelial cell membranes may also apply to respiratory gas exchanges in lung and body tissues. Müller (112) and Pircher (113) developed the mathematical theory of gas diffusion into a limited liquid layer and calculated the diffusion process for oxygen entering water. In highly diluted hemoglobin solutions, oxygen diffusion was found to obey the Fick laws. With higher concentrations (10 per cent) the diffusion constant is reduced to about two thirds of its pure water value. The duration of the nonstationary phase of diffusion increases with hemoglobin concentration according to the increasing oxygen combining power. On the basis of the diffusion theory, Dirken & Heemstra (114, 115) calculated the alveolar-arterial difference in oxygen tension for various oxygen concentrations in the inspired air, provided the deficit gradient be known for one gas mixture. At alveolar oxygen pressures above 100 mm. Hg, diffusion is considered sufficient to approach equilibrium. Galdston & Wollack (116) found on healthy individuals alveolar and arterial oxygen and carbon dioxide tensions of 98 versus 97 mm. Hg and 41 versus 42 mm. Hg, respectively, at rest; and of 115 versus 110 mm. Hg and 41 versus 44 mm. Hg respectively, after moderate exercise. Comparative measurements were made on patients suffering from phosgene poisoning [Galdston *et al.* (117)]. By combining anoxia with exercise Gemmill (118) found a considerable lack of equilibrium between the oxygen tension measured directly in the alveolar air and that determined from oxygen saturation of the arterial blood. Nitrogen elimination of anesthetized dogs continuously inhaling oxygen (99.6 per cent) or oxygen with 5 per cent carbon dioxide at atmospheric pressure has been found by Karel & Weston(119)

to be slower than previously reported in literature. Complete denitrogenation cannot be achieved in resting animals within less than six hours of pure oxygen breathing, allowance being made for diffusion into the body of nitrogen from the surrounding air. Barger *et al.* (120), using a modified Geiger-Müller counter, followed the course of penetration of radioactive argon (A^{37}) into lungs, blood, and tissue on animals and man. Pace *et al.* (121) studied the slowing of carbon monoxide desaturation in man breathing pure oxygen as influenced by age. Half-time of desaturation is increasing by 1 per cent for each year above forty.

Boeri & Vescia (122, 123, 124) applied the theory of intermediary reactions to the oxygenation of hemoglobin. The oxygen dissociation curve of hemoglobin has been analysed by Boeri (125) as to its statistical (hyperbolic) and interaction (sigmoid) components. King *et al.* (126), by forming three independent teams of analysts, succeeded in obtaining very accurate determinations of iron content and oxygen capacity of whole blood (pig and human). Cheymol & Henry (127) could not find any difference in oxygen capacity of blood or hemoglobin between young and adult rabbits. Cordier & Cordier (128) studied the *in vivo* oxyhemoglobin dissociation curve (arterial blood oxygen saturation against alveolar oxygen tension) on open-chest dogs inhaling various concentrations of oxygen, under controlled respiration. After removal of carotid and aortic receptors, the curve was shifted to the right. This may be due to decreased alveolar permeability, but also to anoxic acidosis developing to a greater extent in animals deprived of vascular receptors. Cordier & Cordier (129, 130) have further shown that tissue disintegration products originating in a phosgene-poisoned lung have a similar effect on the oxyhemoglobin dissociation curve of the perfusing blood analysed *in vitro*.

Normal oxygen saturation of human arterial blood as determined by Comroe & Walker (131) with an *in vivo* equilibration technique averages 97.5 per cent. Preston & Ordway (132) draw attention to the fact that oxygen physically dissolved in arterial blood may not reach the amount theoretically expected. Further data on arterial and venous oxygen capacity and saturation under various physiological, experimental, and pathological conditions have been reported by several authors (133 to 137), and improved techniques have been described (128 to 146). Baumberger (147),

Heemstra (115), and Wiesinger (148, 149) developed the polarographic method for measuring oxygen tension of whole blood. Studies on diffusion respiration have been continued by Spencer *et al.* (150) measuring oxygen uptake, fall of intrapulmonic pressure, and absorption of carbon monoxide. Whitehead *et al.* (151) studied renal changes and Goldensohn *et al.* (152) electrical cortical activity during and after periods of diffusion respiration. Draper *et al.* (153) determined alveolar gas tensions and venous blood pH in this condition. Binet & Strumza (154) found plasma carbon dioxide accumulation up to 90 volume per cent and maintained life, by preventing lung collapse, for as long as four hours. The survival in pure nitrogen of dogs receiving arterial blood from donor animals has been reported by Binet & Burstein (155). Previous denitrogenation has not been found by Weston & Karel (156) to avoid bubble formation following intravenous administration of oxygen to dogs. Intravenous oxygen is used therapeutically by Gabrici (157).

Wolvekamp & Kruyt (158, 159) report earlier experiments on carbon dioxide dissociation curves and pH of the blood of snail, crab, and lobster, confirming absence of carbonic anhydrase and showing that only bicarbonate and no carbamino compound is formed. The carbon dioxide content of maternal and fetal sheep blood has been determined by Barron (160). Gould *et al.* (161) measured the rate of carbon dioxide elimination following administration of C^{14}-labelled bicarbonate. Respiratory alkalosis from chronic hyperventilation in normal subjects has been studied by Hemingway *et al.* (162), its effects on oxygen saturation of hemoglobin, by Meda & Alella (163). Resulting tissue anoxia is discussed by Carryer (164), whereas Lenggenhager (165) tries to explain why hyperventilation with air or oxygen cannot produce tissue anoxia.

Insufficient respiratory gas exchange and its influence on blood gas content has been investigated by several authors (166 to 172). Hall (173) studied pulmonary gas exchange as related to altitude acclimatization. Herber (174) distinguishes respiratory and superimposed metabolic components of acidosis developing in anesthetized dogs during asphyxiation and questions the advisability of using carbogen in resuscitation from any form of obstructive asphyxia. The effects of various physiological factors on breath-holding time are dealt with by Mitolo (16), Otis *et al.* (104), Vacca & Boeri (175), and Rodbard (176).

Chemical Regulation of Respiration

The carbon dioxide stimulating effect on pulmonary ventilation is largely dependent upon anesthesia and anesthetics as shown by Chapin & Rahn (177) on the beaver, and by Wang & Nims (178) on the cat. It is considerably reduced by ergotamine [Liljestrand (179)]. Gollwitzer-Meier & Pinotti (180) found on dog and man a positive after-effect of the central stimulating action of carbon dioxide on respiration. From studying man's respiratory response during acclimatization to high altitudes, Rahn & Otis (181) conclude that the reduced alkali reserve renders the respiratory center more sensitive to carbon dioxide. Somewhat similar observations have been made by Gollwitzer-Meier (182) on dog and man during the hypopneic breathing following a period of anoxic hyperpnea. Döring & Loeschcke (183) found increased response of respiration to carbon dioxide during pregnancy. According to Heerhaber *et al.* (184), direct action of progesterone on the respiratory center accounts for that increase. The effects of carbon dioxide, anoxia, and cyanide on fetal respiratory movements of the sheep have been studied by Barcroft & Karvonen (185) and found to be due probably to carotid body reflexes. Asphyxia, however, seems not responsible for the onset of breathing at birth. Dahlström *et al.* (186), comparing on human subjects the effects of breathing anoxic or carbon monoxide gas mixtures, confirmed the view that anoxic hyperventilation depends on actual oxygen tension and not on the oxygen combining power of the blood. Sillani (187) measured anoxic hyperventilation during rebreathing and found it setting in earlier, at a somewhat higher oxygen pressure, and becoming greater in anoxia-trained than in untrained subjects. Cheyne-Stokes breathing has been studied in relation to arterial blood saturation by Alella & Meda (188, 189)

Evidence for a direct excitatory action of moderate anoxia on respiratory center may be drawn from comparative results obtained by Cordier & Cordier (190) on chloralosized dogs, with and without aortic and carotid chemoreceptors. Extensive measurements of pulmonary ventilation on dogs under chloralose anesthesia and in various physiological conditions have been reported by Strumza (191).

Sass-Kortsák *et al.* (192) have shown that carbon dioxide as well as oxygen lack increase the mean lung volume, thus shifting respiration to the inspiratory side. Anoxia appears to be more effec-

tive, since it increases functional residual air. But this may only be due to the difference in type of hyperventilation. Heymans & Jacob (193) recorded on dogs the decrease of inspiratory tonus under artificial respiration and its recovery due to humoral changes during the ensuing period of apnea.

Oxygen breathing as studied in man by Alveryd & Brody (194) increases tidal volume and somewhat also respiratory rate and decreases slightly vital capacity. On dog and human breathing oxygen, Gollwitzer-Meier (195) found initial hypopnea with secondary hyperpnea, the latter being the only reaction in animals without chemoreceptors. Oxygen hyperpnea shows a marked positive after-effect of several minutes' duration. Oxygen hypopnea occurs as a fugitive reaction in dogs anesthetized with chloralose, as stated by Binet & Strumza (196), but does not take place after the anesthetic is dissipated. Respiratory depression due to the onset of oxygen breathing following a short period of anoxia has been recorded on patients by Franck *et al.* (197).

Evidence in favour of a chemical mechanism involved in respiratory adaptation to muscular exercise has been presented by Euler & Liljestrand (198) studying the effect of electrical stimulation of a denervated limb on the chloralose anesthetized animal and by Heymans *et al.* (199) using the perfused isolated head technique. During moderate muscular work oxygen-want as well as carbon dioxide stimulate respiration both directly and through chemoreceptors. Combined effects of exercise and carbon dioxide on pulmonary ventilation in man have been investigated by Craig *et al.* (200).

Reflex Control of Respiratory Posture and Movement

Attempts have been made during the past year tending to a better understanding of the vagal afferents concerned with respiratory control. Whitteridge (201) studying the responsiveness of pulmonary stretch receptors in phosgene-poisoned cats found no relative increase in the frequency response of single vagal stretch fibres to inflation of the lungs, as occurs with volatile anesthetics; but along with the respiratory lung volume changes, stretch impulse frequencies do not rise as much as in control experiments and show a more marked tendency to adaptation. This may explain to some extent the respiratory reaction to acute phosgene inhala-

tion, i.e., its inspiratory predominance. For with a relative loss of higher afferent frequencies, the normal expiratory or inspiratory-inhibitory reflex is less pronounced [Wyss (202)]. Confirming results have been obtained by Bucher & Schneider (203) and Bucher (204) with local anesthetics preventing pulmonary stretch receptors from discharging at the usual higher frequencies during lung inflation and thus lessening expiratory, while accentuating inspiratory, reactions. Injury to pulmonary stretch receptors may also be responsible for the rapid shallow breathing observed by Galdston *et al.* (205) on patients suffering from residual effects after acute exposure to phosgene, as well as for the polypnea described by Wilson & Samaan (206), and by Walsh (207) as resulting from multiple pulmonary embolism and which is abolished by vagotomy. Torrance & Whitteridge (208), however, obtained rapid breathing following intravenous starch injection or lung deflation even after conduction of stretch impulses had been blocked by cooling both vagi at plus 6°C. Thus receptors other than ordinary stretch endings may also be involved in respiratory reflexes originating in the lungs. Whitteridge (209) identified three types of cardiovascular afferent fibres present in the vagus and considers the second group of intrapulmonic vascular pressoreceptors as playing a part in the lung deflation reflex. Those pulmonary vascular fibres withstand cooling down to plus 6°C. They accelerate breathing reflexly and would account to a considerable extent for polypnea to embolism or other lung injury. The complexity of respiratory reactions, and especially of those accompanied by increased rate of breathing, may thus be explained by a combined action of different types of lung receptors. Stimulating the afferent vagus nerve in the monkey, Wyss (210) was able to distinguish two forms of respiratory acceleration: one is associated with weak stimuli producing a slight inspiratory reaction and is considered as the artificial equivalent of a pure Hering-Breuer deflation reflex; the other occurs with stronger stimuli and shows increased amplitude and ventilation, resembling a more general and less specific activation of respiration as it is known from chemoreceptor or pain stimulation; it may also be related to pulmonary vascular pressoreceptors. Clinical interest is directed to vagal afferents from heart and lung by observations on respiratory disorders such as those reported by Wolf (211).

Mechanical and vagal reflex components involved in respiratory postural reactions have been studied by Moruzzi (212) on

rabbits. Bucher (213) measured the inspiratory phase prolongation following tracheal occlusion and found it mainly a lung volume reflex, yet modified by an alleged reaction against obstructive resistance. Saris *et al.* (214) describe a thoracic wall reflex, obtainable on dogs with respiratory movements stopped by pentothal; as it was abolished by vagotomy, it must be of pulmonary origin.

Wyss and co-workers (215 to 219) succeeded in locating separate centers in the rabbit's medulla oblongata for the expiratory [Andereggen *et al.* (215)] and inspiratory [Oberholzer *et al.* (217)] component of vagal respiratory reflexes lying at a higher and lower level, respectively, within the caudal part of the solitary tract and surrounding gray matter. By stimulation of this same region in the cat's lower brain stem, Borison *et al.* (220) obtained spasmodic respiratory activity. The varying responsiveness of the respiratory center to stimulation of the afferent vagus and laryngeal nerves has been studied by Lueken & Timm (221) and by Larrabee & Hodes (222), respectively; its escape from inhibiting stimulation of both these nerves was studied by Cier *et al.* (223, 224). Vagal afferents of the Hering-Breuer type were also found to be active in producing or inhibiting the crossed phrenic phenomenon [Chatfield & Mead (225)]. Fleisch (226) and Dolivo (227) further investigated the role played by the motor roots of the phrenic nerve in conductin afferent impulses controlling respiratory movements. Kohrman *et al.* (228) obtained respiratory activation by stimulating afferent fibers within the phrenic nerve.

Respiratory Center and Higher Control

The spontaneous rhythmic activity of the respiratory center as recorded on a curarized animal by the phrenic nerve's action currents persists after removal of all chemoreceptors [Winterstein (229, 230)]. By partial destruction within the respiratory center of a median region lying at the level of the calamus scriptorius, Rijlant (231) was able to eliminate his so-called modulating center, thus depriving the phrenic motoneurons of a steady excitatory drive necessary for the efferent respiratory exteriorization and leaving them under only the influence of the rhythmically active fundamental center. "Occult" respiration ensues, which can again be rendered manifest by activating the motoneurons directly through continuous repetitive stimulation. Rijlant (232, 233) further distinguished two different forms of conditioning inspiratory moto-

neuron activity from stimulating lateral and medial descending paths in the lateral funiculus of the cord. Evidence of to and fro irradiation between respiratory and somatic motor centers will be found in observations reported by Vinokurov (234) and Saunders (235). Isolated labyrinthine stimuli, as studied by Finocchi (236) on the pigeon, were found to remain without any effect on respiraation.

Activation or inhibition of the respiratory center as obtained by Bach (237) from stimulation of bulbar and pontine reticular substance can only be regarded as a nonspecific component in a comprehensive regulation controlling somatic and autonomic functions in general. From higher meso- and diencephalic levels Hess & Müller (238) obtained by adequate electrical stimulation of various regions distinctly different respiratory effects of apparent physiological significance [Hess (239, 240)]. Marked respiratory responses resembling those from vagal stimulation have been obtained by Delgado & Livingston (241) and Sachs & Brendler (242) on stimulating the orbital cortex of the frontal lobe in dog and monkey. Expiratory as well as inspiratory reactions have been observed and respiratory movement could be inhibited in any phase of its development. The posteriomedial portion of the monkey's orbital gyrus seems particularly effective.

Comparative analysis of the development of thermal polypnea in normal, spinal, and decerebrate dogs enabled Bonvallet *et al.* (243) and Bonvallet & Dell (244, 245, 246) to distinguish three different reactions of the respiratory center, i.e., a local temperature effect, a bulbar "tachypneic" factor, and the well-known diencephalic panting response. Hall *et al.* (247) determined the rectal temperature at which thermal polypnea appears and found it elevated by about 2°C. following typhoid-paratyphoid vaccine injection. But the respiratory response to carbon dioxide is not depressed by the vaccine. Magnesium chloride lowers the temperature level for polypneic heat defense. Thermal paralysis of the respiratory center under air and oxygen breathing has been investigated by Binet & Strumza (248).

Robinson & Gantt (249) draw attention to the respiratory component in conditioned "orienting" or "focussing" reflexes. Corey (250) examining pilots in the Link-trainer and airplanes noted increasing metabolism and respiratory rate with growing flight task complexity.

Miscellaneous

Chemical and pharmacological effects on the respiratory center are dealt with in a series of papers (251 to 267). Several authors (268 to 275) have contributed to comparative physiology of respiration.

A method for measuring respiratory volumes of laboratory animals is described by Guyton (276) and one for continuous recording of expired air volume on human subjects, by Scott & Worth (277). Von Tavel (278) developed a low resistance respiratory valve and an automatically compensated spirograph refilling device. Improved techniques for analysis of respiratory and blood gases are reported by various investigators (100 to 108, 115, 120, 133, 136, 139 to 149, 162, 279, 280, 281). The Burns pneumatic balance resuscitator is described by Jacobs (98, 99), aircraft oxygen equipment by Berner & Good (282), maintenance of prescribed oxygen and carbon dioxide concentrations in closed head tents by Barach (283), and the principle of the chemical oxygen generator by Millikan & Pappenheimer (284). Carlson *et al.* (285) announce a new apparatus for the measurement of pulmonary function for general, clinical, and experimental tests.

LITERATURE CITED

1. Hitchcock, F. A., and Whitehorn, W. V., *Ann. Rev. Physiol.*, **10**, 277–304 (1948)
2. Herlitzka, A., *Riv. med. aeronaut.*, **10**, 97–109 (1947)
3. Brown, E. A., *Ann. Allergy*, **5**, 381–91 (1947)
4. Malméjac, J., *Médecine de l'aviation. Bases physiologiques et physiopathologiques*, 333 pp. (Masson et Cie, Paris, 1948)
5. Policard, A., *Compt. rend.*, **224**, 874–77 (1947)
6. Policard, A., *Bull. histol. appl. physiol. et path. et tech. microscop.*, **24**, 127–31 (1947)
7. Mack, I., Grossman, M., and Katz, L. N., *Am. J. Physiol.*, **150**, 654–60 (1947)
8. Heyer, H. E., Holman, J., and Shires, G. T., *Am. Heart J.*, **35**, 463–79 (1948)
9. Lindskog, G. E., and Gilman, A., *Am. J. Physiol.*, **152**, 417–22 (1948)
10. Campbell, G. S., and Harvey, R. B., *Am. J. Physiol.*, **152**, 671–73 (1948)
11. Grailly, R. de, and Marchal, J., *Union méd. Paris*, **28**, 67–71 (1948)
12. Veen, H., *Arch. néerl. Physiol.*, **28**, 451–61 (1947)
13. Caruso, A., and Stassi, M., *Boll. soc. ital. biol. sper.*, **23**, 508–9 (1947)
14. Donno, L., *Gazz. med. ital.*, **106**, 222–24 (1947)
15. Wiggers, C. J., Levy, M. N., and Graham, G., *Am. J. Physiol.*, **151**, 1–12 (1947)
16. Mitolo, M., *Fisiol. e med.*, **1**, 103–11 (1947)

17. SOKALCHUK, A., ELLIS, D., AND GREISHEIMER, E. M., *Federation Proc.*, **7**, 118 (1948)
18. ROWINSKI, P., AND TALENTI, C., *Arch. sci. biol. (Italy)*, **31**, 39-62 (1946)
19. OTIS, A. B., AND PROCTOR, D. F., *Am. J. Physiol.*, **152**, 106–12 (1948)
20. SPECHT, H., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 119–20 (1947)
21. GIERKE, H. VON, *Arch. ges. Physiol. (Pflügers)*, **249**, 307–12 (1947)
22. SLOAN, J. Q., BAIN, G. P., AND BRUCER, M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 264–67 (1947)
23. TALBOT, T. R., QUIMBY, E. H., AND BARACH, A. L., *Am. J. Med. Sci.*, **214**, 585–92 (1947)
24. POLICARD, A., *Experientia*, **4**, 113–14 (1948)
25. BINET, L., AND BURSTEIN, M., *J. physiol. et path. gén.*, **39**, 7–33 (1946–47)
26. HALPERN, B. N., HAMBURGER, J., MILLIEZ, P., AND DOMART, A., *Compt. rend. soc. biol.*, **141**, 479–82 (1947)
27. SIEGMUND, O. H., GRANGER, H. R., AND LANDS, A. M., *J. Pharmacol. Exptl. Therap.*, **90**, 254–59 (1947)
28. LERMAN, S., AND GOLDFEDER, A., *Compt. rend. soc. biol.*, **141**, 446–47 (1947)
29. BENDA, R., BENDA, P., MAROGER, M., AND PAILLAS, J., *Bull. Soc. med. Hôp., Paris*, **63**, 385–90 (1947)
30. CASTILLO, J. C., AND DE BEER, E. J., *J. Pharmacol. Exptl. Therap.*, **90**, 104–9 (1947)
31. CASTILLO, J. C., *Federation Proc.*, **7**, 210–11 (1948)
32. HEYMANS, C., AND JACOB, J., *Arch. intern. pharmacodynamie*, **74**, 233–52 (1947)
33. LANDMESSER, C. M., *Anesthesiology*, **8**, 506–23 (1947)
34. MINET, J., FONTAN, M., AND BONDUELLE, A., *Presse méd.*, **55**, 389–91 (1947)
35. BARACH, A. L., AND GARTHWAITE, B., *Ann. Allergy*, **5**, 297–316 (1947)
36. WYSS, F., *Helv. Med. Acta*, **14**, 413–16 (1947)
37. VISSCHER, M. B., *Federation Proc.*, **7**, 128 (1948)
38. BRUNER, H. D., AND SCHMIDT, C. F., *Am. J. Physiol.*, **148**, 648–66 (1947)
39. DE BUSSCHER, G., *Bull. histol. appl. physiol. et path. et tech. microscop.*, **24**, 193–207 (1947)
40. PRINZMETAL, M., ORNITZ, E. M., SIMKIN, B., AND BERGMAN, H. C., *Am. J. Physiol.*, **152**, 48–52 (1948)
41. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR., *Bull. Johns Hopkins Hosp.*, **80**, 107–20 (1947)
42. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR., *Bull. Johns Hopkins Hosp.*, **80**, 121–41 (1947)
43. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR., *Bull. Johns Hopkins Hosp.*, **80**, 323–47 (1947)
44. VANDAM, L. D., BING, R. J., AND GRAY, F. D., JR., *Bull. Johns Hopkins Hosp.*, **81**, 192–215 (1947)
45. GRAY, F. D., JR., BING, R. J., AND VANDAM, L. D., *Am. J. Physiol.*, **151**, 245–51 (1947)
46. COURNAND, A., MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D., AND BALDWIN, J., *Am. J. Physiol.*, **150**, 267–71 (1947)
47. COURNAND, A., *Bull. N. Y. Acad. Med.*, **23**, 27–50 (1947)

48. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A., *Am. J. Physiol.*, **152**, 372–82 (1948)
49. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D., *Am. J. Physiol.*, **150**, 315–20 (1947)
50. Euler, U. S. v., and Liljestrand, G., *Abstracts Intern. Physiol. Congr. 17th Congr., Oxford*, 145 (1947)
51. Logaras, G., *Acta Physiol. Scand.*, **14**, 120–35 (1947)
52 Burstein, M., *J. physiol. et path. gén.*, **39**, 75–86 (1946–47)
53. Brown, F., and Rodbard, S., *Federation Proc.*, **7**, 15 (1948)
54. Bakos, A. C. P., *Federation Proc.*, **7**, 204 (1948)
55. Smith, J. R., and Hara, M., *Federation Proc.*, **7**, 117 (1948)
56. Bageant, W. E., and Raper, L. A., *Anesthesiology*, **8**, 500–5 (1947)
57. Parin, V. V., *Am. J. Med. Sci.*, **214**, 167–75 (1947)
58. Howarth, S., McMichael, J., and Sharpey-Schafer, E. P., *Brit. Heart J.*, **9**, 292–303 (1947)
59. Hickam, J. B., and Cargill, W. H., *J. Clin. Invest.*, **27**, 10–23 (1948)
60. Basu, M. N., *Calcutta Med. Rev.*, **14**, 103–7 (1947)
61. Brannon, E. S., *Proc. Am. Federation Clin. Research*, **3**, 103 (1947)
62. Lenègre, J., and Maurice, P., *Arch. mal. coeur*, **40**, 173–78 (1947)
63. Vogel, H., *Helv. Physiol. et Pharmacol. Acta*, **5**, 105–21 (1947)
64. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sagerson, R. P., and Evans, J. M., *J. Clin. Invest.*, **26**, 554–60 (1947)
65. Policard, A., *Bull. histol. appl. physiol. et path. et tech.*, **24**, 60–69 (1947)
66. Whiteleather, J. E., and Gardner, J. E., *J. Tenn. State Med. Assoc.*, **40**, 326–29 (1947)
67. Koenig, H., and Koenig, R., *Federation Proc.*, **7**, 67 (1948)
68. Drinker, C. K., and Hardenbergh, E., *Federation Proc.*, **7**, 29 (1948)
69. Latta, H., *Bull. Johns Hopkins Hosp.*, **80**, 181–97 (1947)
70. Cameron, G. R., and Courtice, F. C., *J. Physiol.* (*London*), **105**, 175–85 (1946–47)
71. Hebb, C., and Nimmo-Smith, R. H., *J. Physiol.* (*London*), **105**, 1–15 (1946–47)
72. Courtice, F. C., and Phipps, P. J., *J. Physiol.* (*London*), **105**, 186–90 (1946–47)
73. Surtshin, A., Katz, L. N., and Rodbard, S., *Am. J. Physiol.*, **152**, 589–90 (1948)
74. Daly, I. de B., Duke, H., and Weatherall, J. *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 12–13 (1947)
75. Daly, I. de B., and Duke, H., *Quart. J. Exptl. Physiol.*, **34**, 151–58 (1948)
76. Brecht, K., *Arch. ges. Physiol.* (*Pflügers*), **249**, 94–111 (1947)
77. Elwell, L. E., and Bean, J. W., *Federation Proc.*, **7**, 31 (1948)
78. Holldack, K., *Klin. Wochschr.*, **24/25**, 566 (1946–47)
79. Henry, J. P., Jacobs, H., Meeham, H., and Karstens, A., *Federation Proc.*, **7**, 53 (1948)
80. Jacobs, H., Karstens, A., and Henry, J. P., *Federation Proc.*, **7**, 60–61 (1948)
81. Fenn, W. O., Otis, A. B., Rahn, H., Chadwick, L. E., and Hegnauer, A. H., *Am. J. Physiol.*, **151**, 258–69 (1947)
82. Fenn, W. O., and Chadwick, L. E., *Am. J. Physiol.*, **151**, 270–75 (1947)

83. De Lalla, V., *Am. J. Physiol.*, **152**, 122–30 (1948)
84. Gilliatt, R. W., *J. Physiol.* (*London*), **107**, 76–88 (1948)
85. Gilliatt, R. W., Guttmann, L., and Whitteridge, D., *J. Physiol.* (*London*), **107**, 67–75 (1948)
86. Drury, D. R., Henry, J. P., and Goodman, J., *J. Clin. Invest.*, **26**, 945–51 (1947)
87. Adler, H. F., *Quart. Research Rept. U. S. School Aviat. Med.*, 20–22 (1947)
88. Ivy, J. H., and Adler, H. F., *Quart. Research Rept. U. S. School Aviat. Med.*, 22 (1948)
89. Otis, A. B., Suskind, M., and Rahn, H., *Federation Proc.*, **7**, 88–89 (1948)
90. Marchal, M., *Compt. rend.*, **225**, 394–96 (1947)
91. Cournand, A., Motley, H. L., Werko, L., and Richards, D. W., *Am. J. Physiol.*, **152**, 162–74 (1948)
92. Motley, H. L., Werko, L., Cournand, A., and Richards, D. W., *J. Aviation Med.*, **18**, 417–35 (1947)
93. Eckman, M., Barach, B., Fox, C., Rumsey, C. C., Somkin, E., and Barach, A. L., *J. Aviation Med.*, **18**, 565–76 (1947)
94. Papper, E. M., and Reaves, D. P., *Anesthesiology*, **8**, 407–9 (1947)
95. Boche, R. D., Bruner, H. D., Talbot, T. R., McCarthy, M. D., and Gibbon, M. H., *Am. J. Med. Sci.*, **214**, 612–16 (1947)
96. Zinberg, S., Nudell, G., Kubicek, W. G., and Visscher, M. B., *Am. Heart J.*, **35**, 774–79 (1948)
97. Sussman, A. H., Hemingway, A., and Visscher, M. B., *Am. J. Physiol.*, **152**, 585–88 (1948)
98. Jacobs, H. J., *J. Aviation Med.*, **18**, 436–39 (1947)
99. Jacobs, H. J., *Bull. U. S. Army Med. Dep.*, **7**, 707–17 (1947)
100. Fowler, W. S., *Federation Proc.*, **7**, 35 (1948)
101. Boeri, E., and Vacca, C., *Boll. soc. ital. biol. sper.*, **23**, 1063–64 (1947)
102. Lambie, C. G., and Morrissey, M. J., *J. Physiol.* (*London*), **107**, 14–23 (1948)
103. Rahn, H., and Otis, A. B., *Am. J. Physiol.*, **150**, 202–21 (1947)
104. Otis, A. B., Rahn, H., and Fenn, W. O., *Am. J. Physiol.*, **152**, 674–86 (1948)
105. Cordier, D., and Cordier, G., *XVe Réunion Assoc. Physiol. Langue française, Toulouse*, 141–43 (1947)
106. Birath, G., *Am. Rev. Tuberc.*, **55**, 444–48 (1947)
107. Stacy, R. W., Hunter, J. A., and Hitchcock, F. A., *Federation Proc.*, **7**, 120 (1948)
108. Blinn, K. A., and Noell, W. K., *Quart. Research Rept. U. S. School Aviat. Med.*, 6 (1948)
109. Galdston, M., and Horwitz, S. A., *Federation Proc.*, **7**, 39–40 (1948)
110. Oglialoro, C. M., *Boll. soc. ital. biol. sper.*, **23**, 990–92 (1947)
111. Sturm, H., *Arch. ges. Physiol.* (*Pflügers*), **249**, 480–93 (1947)
112. Müller, A., *Helv. Physiol. et Pharmacol. Acta*, **6**, 21–41 (1948)
113. Pircher, L., *Inaugural Dissertation* (*Freiburg, Schweiz*, 1948)
114. Dirken, M. N. J., and Heemstra, H., *Arch. néerland. physiol.*, **28**, 501–9 (1947)
115. Heemstra, H., *Alveolaire Zuurstofspanning en Longcirculatie*, 178 pp. (Doctoral Thesis, R¨ks-Universiteit, Groningen, 1948)
116. Galdston, M., and Wollack, A. C., *Am. J. Physiol.*, **151**, 276–81 (1947)

117. GALDSTON, M., LUETSCHER, J. A., LONGCOPE, W. T., BALLICH, N. L., KREMER, V. L., FILLEY, G. L., AND HOPSON, J. L., *J. Clin. Invest.*, **26**, 169–81 (1947)
118. GEMMILL, C. L., *J. Aviation Med.*, **18**, 483–94 (1947)
119. KAREL, L., AND WESTON, R. E., *Am. J. Physiol.*, **151**, 71–79 (1947)
120. BARGER, A. C., RICHARDSON, G. S., AND LANDIS, E. M., *Federation Proc.*, **7**, 5 (1948)
121. PACE, N., STRAJMAN, E., AND WALKER, E., *Federation Proc.*, **7**, 89 (1948)
122. BOERI, E., AND VESCIA, A., *Arch. néerl. physiol.*, **28**, 510–20 (1947)
123. BOERI, E., AND VESCIA, A., *Arch. intern. physiol.*, **55**, 153–62 (1947)
124. BOERI, E., AND VESCIA, A., *Boll. soc. ital. biol. sper.*, **23**, 238–40 (1947)
125. BOERI, E., *Experientia*, **4**, 29–31 (1948)
126. KING, E. J., GILCHRIST, M., WOOTTON, I. D. P., O'BRIEN, J. R. P., JOPE, H. M., QUELCH, P. E., PETERSON, J. M., STRANGEWAYS, D. H., AND RAMSAY, W. N. M., *Lancet*, **254**, 478–83 (1948)
127. CHEYMOL, J., AND HENRY, R., *Bull. soc. chim. biol.*, **29**, 81–86 (1947)
128. CORDIER, D., AND CORDIER, G., *XVe Réunion Assoc. Physiol. Langue française, Toulouse*, 137–40 (1947)
129. CORDIER, D., AND CORDIER, G., *Compt. rend. soc. biol.*, **142**, 93–95 (1948)
130. CORDIER, D., AND CORDIER, G., *Compt. rend. soc. biol.*, **142**, 95–97 (1948)
131. COMROE, J. H., AND WALKER, P., *Am. J. Physiol.*, **152**, 365–71 (1948)
132. PRESTON, S. N., AND ORDWAY, N. K., *Am. J. Physiol.*, **152**, 696–702 (1948)
133. SNYDER, F. F., *Federation Proc.*, **7**, 118 (1948)
134. FOWLER, W. S., AND COMROE, J. H., *Am. J. Med. Sci.*, **215**, 109 (1948)
135. PENNEYS, R., AND THOMAS, C. B., *Bull. Johns Hopkins Hosp.*, **82**, 470–78 (1948)
136. MILLER, R. A., HEAGAN, B. S., AND TAYLOR, C. B., *Am. J. Physiol.*, **150**, 1–6 (1947)
137. GRECO, G., *Boll. soc. ital. biol. sper.*, **24**, 1–3 (1948)
138. WOOD, E. H., GERACI, J. E., AND GROOM, D. L., *Federation Proc.*, **7**, 137 (1948)
139. MONTGOMERY, G. E., GERACI, J. E., AND WOOD, E. H., *Federation Proc.*, **7**, 81 (1948)
140. WOOD, E. H., MONTGOMERY, G. E., AND GERACI, J. E., *Federation Proc.*, **7**, 137 (1948)
141. GERACI, J. E., MONTGOMERY, G. E., AND WOOD, E. H., *Federation Proc.*, **7**, 41 (1948)
142. BEHRMANN, V. G., *Federation Proc.*, **7**, 7 (1948)
143. COMROE, J. H., AND BOTELHO, S., *Am. J. Med. Sci.*, **214**, 1–6 (1947)
144. MEIER, R., PELLMONT, B., AND WIRZ, E., *Helv. Physiol. et Pharmacol. Acta*, **5**, C43 (1947)
145. SCHOLANDER, P. F., AND IRVING, L., *J. Biol. Chem.*, **169**, 561–69 (1947)
146. GRANT, W. C., *Proc. Soc. Exptl. Biol. Med.*, **66**, 60–62 (1947)
147. BAUMBERGER, J. P., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 173–74 (1947)
148. WIESINGER, K., *Helv. Physiol. et Pharmacol. Acta*, **6**, C13–C14 (1948)
149. WIESINGER, K., *Helv. Physiol. et Pharmacol. Acta*, **6**, C34–C35 (1948)
150. SPENCER, J. N., DRAPER, W. B., PARRY, T. M., AND WHITEHEAD, R. W., *Federation Proc.*, **7**, 119–20 (1948)

151. WHITEHEAD, R. W., BESHORE, D. L. G., DRAPER, W. B., SPENCER, J. N., AND PARRY, T. M., *Federation Proc.*, **7**, 264–65 (1948)
152. GOLDENSOHN, E. S., BUSSE, E. W., SPENCER, J. N., DRAPER, W. B., AND WHITEHEAD, R. W., *Federation Proc.*, **7**, 223 (1948)
153. DRAPER, W. B., WHITEHEAD, R. W., AND SPENCER, J. N., *Anesthesiology*, **8**, 524–33 (1947)
154. BINET, L., AND STRUMZA, M. V., *Compt. rend.*, **225**, 12–14 (1947)
155. BINET, L., AND BURSTEIN, M., *Compt. rend. soc. biol.*, **141**, 250–51 (1947)
156. WESTON, R. E., AND KAREL, L., *J. Clin. Invest.*, **26**, 837–48 (1947)
157. GABRICI, E., *Minerva med.*, **38**, 380–86 (1947)
158. WOLVEKAMP, H. P., AND KRUYT, W., *Arch. néerl. Physiol.*, **28**, 620–29 (1947)
159. WOLVEKAMP, H. P., AND KRUYT, W., *Bull. soc. chim. biol.*, **29**, 50–52 (1947)
160. BARRON, D. H., *Federation Proc.*, **7**, 6 (1948)
161. GOULD, R. G., ROSENBERG, I. M., SINEX, M., AND HASTINGS, A. B., *Federation Proc.*, **7**, 156–57 (1948)
162. HEMINGWAY, A., BROWN, E. B., CAMPBELL, G. S., GOLLAN, F., AND ELAM, J. O., *Federation Proc.*, **7**, 52 (1948)
163. MEDA, E., AND ALELLA, A., *Boll. soc. ital. biol. sper.*, **23**, 272–75 (1947)
164. CARRYER, H. M., *Proc. Staff Meetings Mayo Clin.*, **22**, 456–64 (1947)
165. LENGGENHAGER, K., *Helv. Med. Acta*, **14**, 137–73 (1947)
166. ROSSIER, P. H., WIESINGER, K., AND BÜHLMANN, A., *Helv. Med. Acta*, **14**, 404–6 (1947)
167. VERZÁR, F., AND VOEGTLI, W., *Schweiz. med. Wochschr.*, **77**, 980–82 (1947)
168. JANTON, O. H., REDONDO, H. P., AND SCOTT, J. C., *Federation Proc.*, **7**, 61 (1948)
169. COLLDAHL, H., *Acta Med. Scand.*, **128**, 417–27 (1947)
170. KURSHAKOV, N. A., AND SHARAFIAN, M. A., *Klin. Med.* (*U. S. S. R.*), **25**, 36–45 (1947)
171. TETELBAUM, A. G., *Klin. med.* (*U. S. S. R.*), **25**, 45–52 (1947)
172. PASARGIKLIAN, M., AND DAL COLLO, F., *Boll. soc. ital. biol. sper.*, **23**, 95–97 (1947)
173. HALL, F. G., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 111 (1947)
174. HERBER, F. J., *Am. J. Physiol.*, **152**, 687–95 (1948)
175. VACCA, C., AND BOERI, E., *Riv. med. aeronaut.*, **10**, 3–9 (1947)
176. RODBARD, S., *Am. J. Physiol.*, **150**, 142–48 (1947)
177. CHAPIN, J. L., AND RAHN, H., *Federation Proc.*, **7**, 19–20 (1948)
178. WANG, S. C., AND NIMS, L. F., *J. Pharmacol. Exptl. Therap.*, **92**, 187–95 (1948)
179. LILJESTRAND, A., *Acta Physiol. Scand.*, **15**, 198–206 (1948)
180. GOLLWITZER-MEIER, K., AND PINOTTI, O., *Arch. ges. Physiol.* (*Pflügers*), **249**, 3–16 (1947)
181. RAHN, H., AND OTIS, A. B., *Federation Proc.*, **7**, 96–97 (1948)
182. GOLLWITZER-MEIER, K., *Arch. ges. Physiol.* (*Pflügers*), **249**, 17–31 (1947)
183. DÖRING, G. K., AND LOESCHCKE, H. H., *Arch. ges. Physiol.* (*Pflügers*), **249**, 437–51 (1947)
184. HEERHABER, I., LOESCHCKE, H. H., AND WESTPHAL, U., *Arch. ges. Physiol.* (*Pflügers*), **250**, 42–55 (1948)
185. BARCROFT, J., AND KARVONEN, M. J., *J. Physiol.* (*London*), **107**, 153–61 (1948)

186. DAHLSTRÖM, H., OBRESCHKOW, G., AND SJÖSTRAND, T., *Acta Pharmacol. Toxicol*, **3**, 105–23 (1947)
187. SILLANI, L. S., *Riv. med. aeronaut.*, **10**, 499–510 (1947)
188. ALELLA, A., AND MEDA, E., *Minerva med.*, **38**, 396–402 (1947)
189. MEDA, E., AND ALELLA, A., *Arch. fisiol.*, **47**, 161–72 (1948)
190. CORDIER, D., AND CORDIER, G., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 230–31 (1947)
191. STRUMZA, M. V., *J. physiol. et path. gén.*, **39**, 199–217 (1946–47)
192. SASS-KORTSÁK, A., PEYSER, E., AND VERZÁR, F., *Helv. Physiol. et Pharmacol. Acta*, **5**, C46–C47 (1947)
193. HEYMANS, C., AND JACOB, J., *Arch. internat. pharmacodynamie*, **75**, 382–91 (1948)
194. ALVERYD, A., AND BRODY, S., *Acta Physiol. Scand.*, **15**, 140–49 (1948)
195. GOLLWITZER-MEIER, K., *Arch. ges. Physiol. (Pflügers)*, **249**, 32–43 (1947)
196. BINET, L., AND STRUMZA, M. V., *Compt. rend. soc. biol.*, **141**, 3–5 (1947)
197. FRANCK, C., GRANDPIERRE, R., AND ROYER, P., *Compt. rend. soc. biol.*, **142**, 376–78 (1948)
198. EULER, U. S. v., AND LILJESTRAND, G., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 143–44 (1947)
199. HEYMANS, C., JACOB, J., AND LILJESTRAND, G., *Acta Physiol. Scand.*, **14**, 86–101 (1947)
200. CRAIG, F. N., STUBBS, J., AND MARZULLI, F. N., *Federation Proc.*, **7**, 24 (1948)
201. WHITTERIDGE, D., *J. Physiol. (London)*, **107**, 107–14 (1948)
202. WYSS, O. A. M., *Arch. néerl. physiol.*, **28**, 444–50 (1947)
203. BUCHER, K., AND SCHNEIDER, J., *Helv. Physiol. et Pharmacol. Acta*, **4**, 459–64 (1946)
204. BUCHER, K., *Helv. Physiol. et Pharmacol. Acta*, **5**, 348–60 (1947)
205. GALDSTON, M., LUETSCHER, J. A., LONGCOPE, W. T., BALLICH, N. L., KREMER, V. L., FILLEY, G. L., AND HOPSON, J. L., *J. Clin. Invest.*, **26**, 145–68 (1947)
206. WILSON, W. H., AND SAMAAN, A., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 102–3 (1947)
207. WALSH, E. G., *J. Physiol. (London)*, **106**, 466–70 (1947)
208. TORRANCE, R. W., AND WHITTERIDGE, D., *J. Physiol. (London)*, **107**, 6P–7P (1948)
209. WHITTERIDGE, D., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 224–25 (1947)
210. WYSS, O. A. M., *J. Neurophysiol.*, **10**, 315–20 (1947)
211. WOLF, S., *J. Clin. Invest.*, **26**, 1201 (1947)
212. MORUZZI, G., *Arch. néerl. Physiol.*, **28**, 385–98 (1947)
213. BUCHER, K., *Helv. Physiol. et Pharmacol. Acta.*, **5**, 147–53 (1947)
214. SARIS, D., REED, E. A., AND SCOTT, J. C., *Federation Proc.*, **7**, 108 (1948)
215. ANDEREGGEN, P., OBERHOLZER, R. J. H., AND WYSS, O. A. M., *Helv. Physiol. et Pharmacol. Acta*, **4**, 213–32 (1946)
216. WYSS, O. A. M., ANDEREGGEN, P., AND OBERHOLZER, R. J. H., *Helv. Physiol. et Pharmacol. Acta*, **4**, 443–58 (1946)
217. OBERHOLZER, R. J. H., ANDEREGGEN, P., AND WYSS, O. A. M., *Helv. Physiol. et Pharmacol. Acta*, **4**, 495–512 (1946)

218. WYSS, O. A. M., *Science*, **106**, 322 (1947)
219. WYSS, O. A. M., AND OBERHOLZER, R. J. H., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 360–61 (1947)
220. BORISON, H. L., CLARK, G., AND WANG, S. C., *Federation Proc.*, **7**, 10–11 (1948)
221. LUEKEN, B., AND TIMM, C., *Arch. ges. Physiol. (Pflügers)*, **249**, 241–60 (1947)
222. LARRABEE, M. G., AND HODES, R., *Federation Proc.*, **7**, 69 (1948)
223. CIER, J. F., CHATONNET, J., AND VIAL, J., *Arch. internat. physiol.*, **55**, 236–51 (1947–48)
224. CIER, J. F., AND CHATONNET, J., *Compt. rend. soc. biol.*, **141**, 421–22 (1947)
225. CHATFIELD, P. O., AND MEAD, S., *Federation Proc.*, **7**, 20 (1948)
226. FLEISCH, A., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 146 (1947)
227. DOLIVO, M., *Helv. Physiol. et Pharmacol. Acta*, **4**, 199–212 (1946)
228. KOHRMAN, R. M., NOLASCO, J. B., AND WIGGERS, C. J., *Am. J. Physiol.*, **151**, 547–53 (1947)
229. WINTERSTEIN, H., *Arch. internat. pharmacodynamie*, **73**, 302–4 (1946–47)
230. WINTERSTEIN, H., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 310–11 (1947)
231. RIJLANT, P., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 213–14 (1947)
232. RIJLANT, P., *Arch. internat. pharmacodynamie*, **75**, 462 (1948)
233. RIJLANT, P., *Bull. acad. suisse sci. méd.*, **3**, 367–84 (1948)
234. VINOKUROV, V. A., *J. Physiol. U. S. S. R.*, **31**, 283–93 (1945)
235. SAUNDERS, J. A., *J. Physiol. (London)*, **106**, 25P (1947)
236. FINOCCHI, G., *Boll. soc. ital. biol. sper.*, **24**, 165–68 (1948)
237. BACH, L. M. N., *Federation Proc.*, **7**, 4 (1948)
238. HESS, W. R., AND MÜLLER, H. R., *Helv. Physiol. et Pharmacol. Acta*, **4**, 347–58 (1946)
239. HESS, W. R., *Helv. Physiol. et Physiol. Acta*, Suppl. IV, 1–65 (1947)
240. HESS, W. R., *Die funktionelle Organisation des vegetativen Nervensystems*, 226 pp. (Benno Schwabe, Basel, 1948)
241. DELGADO, J. M. R., AND LIVINGSTON, R. B., *J. Neurophysiol.*, **11**, 39–55 (1948)
242. SACHS, E., AND BRENDLER, S. J., *Federation Proc.*, **7**, 107 (1948)
243. BONVALLET, M., DELL, P., AND VIAL, J., *Compt. rend. soc. biol.*, **141**, 1020–23 (1947)
244. BONVALLET, M., AND DELL, P., *Compt. rend. soc. biol.*, **141**, 1023–24 (1947)
245. BONVALLET, M., AND DELL, P., *Compt. rend soc. biol.*, **142**, 132–35 (1948)
246. BONVALLET, M., AND DELL, P., *Compt. rend. soc. biol.*, **142**, 135–37 (1948)
247. HALL, V. E., GRANT, R., AND FIELD, J., *Federation Proc.*, **7**, 48–49 (1948)
248. BINET, L., AND STRUMZA, M. V., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 176–77 (1947)
249. ROBINSON, J., AND GANTT, W. H., *Bull. Johns Hopkins Hosp.*, **80**, 231–53 (1947)
250. COREY, E. L., *Federation Proc.*, **7**, 23 (1948)
251. WIERZUCHOWSKI, M., SYSA, J., AND TOCZYSKI, T., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 257–58 (1947)
252. BOVET, D., MONOD, J., AND LWOFF, A., *Compt. rend.*, **224**, 1844–46 (1947)

253. HEYMANS, C., DELAUNOIS, A. L., AND JACOB, J., *Arch. internat. pharmacodynamie*, **75**, 392–401 (1948)
254. MILLER, F. R., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 36–37 (1947)
255. FISCHLEWITZ, J., AND BUCHER, K., *Experientia*, **4**, 196–97 (1948)
256. PINEY, J., *Anæsthesia (London)*, **2**, 70 (1947)
257. SWANK, R. L., AND FOLEY, J. M., *J. Pharmacol. Exptl. Therap.*, **92**, 381–96 (1948)
258. SNAPP, F. E., AND ADLER, H. F., *Quart. Research Rept. U. S. School Aviat. Med.*, 23 (1948)
259. GERARD, R. W., *Advance. Mil. Med. Boston*, **2**, 565–87 (1948)
260. BACQ, Z. M., CHARLIER, R., AND PHILIPPOT, E., *Compt. rend. soc. biol.*, **141**, 960–61 (1947)
261. PANNIER, R., AND VERBEKE, R., *Arch. internat. pharmacodynamie*, **74**, 364–77 (1947)
262. GRUBER, C. M., LUPTON, A. M., AND SCOTTI, T. M., *J. Pharmacol. Exptl. Therap.*, **90**, 202–10 (1947)
263. HEYMANS, C., AND VLEESCHHOUWER, G. R., DE, *Arch. internat. pharmacodynamie*, **75**, 307–24 (1948)
264. HAZARD, R., CHEYMOL, J., AND QUINQUAUD, A., *Compt. rend. soc. biol.*, **141**, 152–53 (1947)
265. HAZARD, R., CHEYMOL, J., AND QUINQUAUD, A., *Compt. rend. soc. biol.*, **141**, 370–72 (1947)
266. HAZARD, R., CHEYMOL, J., AND QUINQUAUD, A., *Compt. rend. soc. biol.*, **141**, 372–74 (1947)
267. SEDEFCIYAN, A., AND WINTERSTEIN, H., *Arch. internat. pharmacodynamie*, **73**, 299–301 (1946–47)
268. THORPE, W. H., AND CRISP, D. J., *J. Exptl. Biol.*, **24**, 227–69 (1947)
269. THORPE, W. H., AND CRISP, D. J., *J. Exptl. Biol.*, **24**, 270–303 (1947)
270. CAMBAR, R., *Compt. rend. soc. biol.*, **141**, 310–12 (1947)
271. MEDICA, G., AND RAULLI, M. L., *Arch. fisiol.*, **45**, 173–77 (1946)
272. MEDICA, G., *Arch. fisiol.*, **45**, 178–88 (1946)
273. BOELAERT, R. B., *Arch. internat. pharmacodynamie*, **73**, 305–43 (1946–47)
274. ROMIJN, C., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 95–96 (1947)
275. GUYTON, A. C., *Am. J. Physiol.*, **150**, 78–83 (1947)
276. GUYTON, A. C., *Am. J. Physiol.*, **150**, 70–77 (1947)
277. SCOTT, C. C., AND WORTH, H. M., *J. Lab. Clin. Med.*, **32**, 1496–99 (1947)
278. TAVEL, F. VON, *Helv. Physiol. et Pharmacol. Acta*, **5**, C35–C37 (1947)
279. CASELLA, C. *Boll. soc. ital. biol. sper.*, **23**, 32–34 (1947)
280. CASELLA, C., *Boll. soc. ital. biol. sper.*, **23**, 35–36 (1947)
281. VACCA, C., *Riv. med. aeronaut.*, **10**, 531–38 (1947)
282. BERNER, F. W., AND GOOD, D. R., *J. Aviation Med.*, **19**, 2–11 (1948)
283. BARACH, A. L., *Am. J. Med.*, **3**, 181–84 (1947)
284. MILLIKAN, G. A., AND PAPPENHEIMER, J. R., *J. Aviation Med.*, **19**, 118–19 (1948)
285. CARLSON, L. D., MARTIN, A. W., AND GATTONE, V., *Federation Proc.*, **7**, 18 (1948)

KIDNEY[1,2]

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Introduction

This review covers the two-year period from July, 1946 to June, 1948. The writer must apologize for his failure to include many articles in this review. Some journals have not been available; in other instances, journals have not been available in complete sets. Consequently, many articles must have been omitted. Restriction of space has limited the extent of this review. Arbitrarily excluded are articles dealing primarily with renal metabolism, excretion studies which do not include observations on glomerular filtration or renal blood flow, articles in which the emphasis is primarily on a related field, such as extracellular space, and articles on hypertension.

Methodology

Chemical and physiological procedures for assessing kidney function are of obvious importance. The papers in this section were chosen not only because they presented new methods or suggested improvements on those already in use, but also because they include mention of other similar methods in the literature.

Schweigert (1) discusses microbiological techniques used in the determination of amino acids in the urine. Lemberg & Callaghan (2, 3, 4) give their methods for the estimation of diazotisable amines. Ellinger & Coulson (5) report a method for the estimation of nicotinamide methochloride in human urine. Von Euler (6, 7) has two papers on the determination and identification of piperidine in human and animal urine. Michelsen, Condiff & Keys (8) describe their method for the determination of thiamine in urine.

[1] Dedicated to the late Alexander Woodward Winkler whose intellectual prodding; deft devising of experiments; and sound, stimulating theorizing in the field of renal physiology will always be remembered by his contemporaries.

[2] The Bureau of Medicine and Surgery of the U. S. Navy does not necessarily undertake to endorse views or opinions which are expressed in this paper.

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The estimation of creatinine is of importance in kidney physiology because in dogs and some other species its clearance represents glomerular filtration. Also, in man, elevation of the creatinine concentration in serum or plasma is used clinically to estimate renal damage. Addis, Barrett & Menzies (9) report a simple clinical method for rapid estimation of serum creatinine. An improvement of the dinitrobenzoic-acid method for the determination of creatinine in plasma and urine has been reported by Gukelberger & Wyss (10). Peters (11) and Bonsnes & Taussky (12) have studied the Jaffe reaction for creatinine and suggest refinements in technique for its estimation. Phillips (13) has also studied this reaction and found the Jaffe color to be extremely sensitive to temperature. Consequently, the concentration of color of unknowns and standards must be determined at the same temperature. Further, he has suggested that picric acid be made up in a concentration of 1 per cent (14) since it is a reagent which is usually available in the biochemical laboratory.

The determination of mannitol has been carefully studied by Elkinton (15). Great detail and explicit instructions are given for obtaining as nearly complete recoveries of mannitol in both serum and urine as have been reported to date. Barker & Clark (16) have found that, if mannitol is determined in the presence of *p*-aminohippuric acid, the *p*-aminohippuric reduces the acid potassium iodate and so introduces an error in the determination of mannitol. Further, in their studies they find that the error can be obviated by acetylating the *p*-aminohippuric acid and acidifying the potassium iodate solution with acetic, instead of sulfuric, acid. It would appear that, in previous papers in which hippurate and mannitol have been administered simultaneously, the mannitol clearances would be in error by a varying amount. Landowne & Alving (17) and Dominguez, Corcoran & Page (18) discuss the reliability of glomerular filtration as estimated from a single intravenous injection of mannitol.

Methods for the estimation of conjugates of glucuronic acid in the urine and the effect of certain physiological variations such as diet, administration of amino acids, and effect of liver injury on the excretion of these conjugates have been reported by Deichmann and his collaborators (19 to 23).

Kruhøffer (24, 25) in studies on nephrectomized rabbits assesses the value of inulin as an indicator for the extracellular space.

Engel, Pentz & Engel (26) have utilized the nephrectomized rat for studying changes in the nitrogen metabolism which occur in a short period of time.

Collings, Martin & Walters (27) in a preliminary paper report a procedure whereby the unanesthetized dog can receive a constant long-term intravenous infusion. With their technique, it has been possible to infuse continuously the dog's jugular vein for as long a period as twenty-eight days. Lamson & De Turk (28) report a very satisfactory method for producing controlled hemorrhage to a desired mean systolic blood pressure.

Keith & Osterberg (29) suggest a test for estimating the degree of renal insufficiency in man by following plasma potassium determinations after oral administration of 5 gms. of potassium bicarbonate. Menten, Junge & Green (30) have reported histochemical technique of azo dye coupling for the estimation of alkaline phosphatase in the kidney. Gunton & Burton (31) report a technique for estimation of small amounts of protein in samples of normal urine. The technique utilizes the measurement of surface activity of the protein solution. The removal of nonfermentable reducing substances in the urine by a precipitating agent is the subject of a paper by Dittebrandt, Tenney & West (32), who find that the utilization of ferric sulfate, Lloyd's reagent, and lead carbonate is probably superior to mercury and other methods now in common use. Eggleston, Johnston & Dobriner (33) report two highly sensitive methods for the estimation of glycogenic activity of steroids. McKittrick & Schmidt (34) have improved the benzidine method of Fiske for the estimation of sulfate in urine.

Methods for the determination of urea have been frequent in the past few years. One of the most satisfactory methods is that of Archibald (35), who uses a colorimetric procedure applicable to blood and urine both in animals and in man. A micromethod for the determination of urea has been reported by Kinsey & Robison (36), using a modification of the Conway technique. Mackenzie & du Vigneaud (37) have reported further evidence, by the use of radioactive techniques, that the only source for urea carbon is from carbon dioxide. The heat capacity entropy and free energy of urea have been reported by Ruehrwein & Huffman (38).

Methods for determining uric acid have been reported by Buchanan, Block & Christman (39) and by Wolfson, Levine & Tinsley (40). Wolfson & Levine (41) have reported a procedure

whereby it is possible to evoke a hyperuricemia in normal man. The excretion of nitrogenous products in reptiles has been reported by Khalil (42, 43).

Anatomy

The innervation of the kidney is again receiving more attention. De Muylder (44) has carefully studied the innervation of the kidney in mouse and sheep embryos. Kubicek, Harvey & Kottke (45), as well as Kriss, Futcher & Goldman (46), have reported preliminary papers on the effect of denervation of the kidney on glomerular filtration, renal blood flow, and the filtration fraction. These studies have been related to blood pressure; in the second paper, the excretion of water and chloride was studied in the animals. The observations appear to indicate that epinephrine sensitization does occur in the denervated kidney. It is important that these studies be verified.

The studies of Trueta and his colleagues (47) on the presence of arteriovenous shunts in the kidney have occasioned wide comment. This work was done on rabbits and the conclusions drawn were the result of radiological studies and the direct observation of the appearance of the kidney. Unfortunately, in the reported work of Trueta no studies have been made of extraction of either an agent which would measure glomerular function or an agent which would represent tubular function. However, studies from Van Slyke's laboratory (48) are interpreted to indicate that in profound hemorrhage in dogs an increased portion of the renal blood flow did not traverse such shunts. Likewise, a preliminary paper by Reubi, Schroeder & Williams (49) compares the extraction ratio of *p*-aminohippurate and the extraction of oxygen by the kidney of dogs and by the kidney of man; they conclude that while renal arteriovenous by-passes may at times appear under some conditions they are not of great importance in the total renal circulation; similar conclusions are reached by the Bradleys (77).

Lucké (50) has written an extensive review of the pathology and pathogenesis of renal lesions seen in blackwater fever, crush syndrome, eclampsia, burns, etc., based on material collected by the U. S. Army Medical Corps.

Applied Physiology

Various renal function studies designed to assess stress placed upon the body are certain to be used more and more, for such

studies can be an extremely valuable addition to the armament of individuals seeking to assess the effects of stress caused by conditions simulating those to which jet planes and atomic energy will subject the human body.

Addis and his collaborators have studied the serum urea concentration and serum creatinine concentration in normal individuals on a varying protein intake. They found (51), in 288 determinations of creatinine concentration in ten medical students, that varying the protein intake from 0.5 to 2.5 gm. of protein per kg. body weight had no effect on the serum creatinine. The average of these 288 determinations on ten students was 1.02 mg. serum creatinine per 100 cc. On the other hand (52), as would be expected, they found that the blood urea concentration varied directly as the protein intake. Subjects on intake of 0.5 gm. of protein per kilo body weight averaged 19 mg. of serum urea per 100 cc. When the diet was increased to 1.5 gm. of protein per kg., the urea concentration was 39 mg. per 100 cc. When the protein intake was 2.5 grams per kg. body weight, the average blood urea concentration was 45 mg. per 100 cc. These studies would have been more accurate if the urine output had been maintained above 2 cc. per min. throughout.

The effect of exercise on glomerular filtration and renal blood flow has been studied by Barclay and associates (53) and by White & Rolf (54). The former authors find that exercise, in individuals with a water diuresis, will result in a decrease in renal blood flow and glomerular filtration and an increase in the filtered fraction of the blood during exercise. The latter authors found that, while there was a decrease in inulin and *p*-aminohippurate clearances in exercise in normal individuals, there was no consistent change in the filtered fraction of the blood. Heavy exercise to the point of of exhaustion was found to decrease the hippurate clearance and inulin clearance to 20 per cent of normal, and they found that the values had not returned to normal within an hour after exercise, thus indicating that blood apparently was being shunted from the viscera.

The effects of a "cold pressor test" on glomerular filtration and effective renal plasma flow has been studied by Talso *et al.* (55) in a preliminary paper. In their studies on seven males (presumably normal individuals) glomerular filtration and renal plasma flow were determined before, during, and after immersion of one foot in

ice water at 1°C. for fifteen minutes. In six of the seven subjects they found a decrease in the mannitol and hippurate clearances during the application of the stimulus or within approximately thirty minutes thereafter. The effect did not persist longer than thirty minutes after conclusion of the test. The decrease in glomerular filtration and effective renal plasma flow as compared with their control values averaged 14 and 21 per cent, respectively. It would appear that further work would have to be done before such a test could be used effectively, inasmuch as some subjects had a decrease in their glomerular filtration and renal blood flow while the foot was immersed in ice water and others had a decrease only after the foot had been removed.

Urea clearances were followed by Drury, Henry & Goodman (56) before, during, and after continuous pressure breathing was applied to four subjects for a thirty-minute period. Pressures of 10, 20, 30, and 40 mm. Hg above ambient pressure were utilized. In most instances this degree of pressure breathing does not result in circulatory collapse. However, in these four subjects there was progressive reduction of the urea clearance, reaching 50 to 20 per cent of the normal values, at the higher pressures. Depression persisted from one to two hours after cessation of the pressure-breathing period. Unlike the results in the "cold pressor test," their results were all quite consistent and it appears that a more uniform or reproducible stress is placed upon the individual by subjecting him to continuous pressure breathing than by applying the "cold pressor test."

Renal Function from Fetal Life through Infancy

Several laboratories have devoted considerable effort to the clarification of the development of renal function from its fetal stage, when it is dormant, to that representative of the adult stage. McCance (57) has recently summarized previous studies on the physiology of the kidney in infancy. His work, as well as the work of other authors, is very adequately reviewed. Cutting & McCance (58, 59) have studied the metabolism of kidney slices from newborn and fullgrown rats, pigs, cats, and man. They find that the metabolism is essentially the same in all species. However, there is a distinct difference between the newborn and adult; in the newborn, kidney tissue is apparently much more stable and independent than in the adult organ.

Williamson & Hiatt (60) have studied renal function in fetal and neonatal rabbits using phenolsulfonphthalein as a test agent. In agreement with previous authors, they find that there is very little, if any, renal function at birth. Renal function increases rapidly for the following ten days during which time there is a hundredfold increase in the excretion of phenolsulfonphthalein while the renal mass increases less than twentyfold.

Heller (61) studied renal function in newborn infants and found that, from the age of eight hours to six days following birth, intramuscular doses of posterior pituitary extract (which produced a pronounced inhibition of water diuresis in adults) had only a very slight and fleeting effect on the urinary concentration of newborn infants who were excreting a markedly hypotonic urine. This low sensitivity of the tubules to the antidiuretic hormone is quite striking. The urine concentration was also studied in children by means of freezing-point determinations, and it was found that the urine excreted during the first two days of extra-uterine life is more concentrated than in subsequent samples.

West, Smith & Chasis (62) have studied, in twenty-one normal infants ranging in age from three days to one hundred and ten weeks glomerular filtration, effective renal plasma flow, and maximal tubular excretory capacity. When the observations are related to unit surface area, the adult mean value for glomerular filtration is reached in some infants in ten to twenty weeks, effective renal plasma flow and maximal tubular excretory capacity in thirty weeks. They suggest that a disproportionately large glomerular surface and increased glomerular pressure are responsible for the precocity of glomerular function rather than a relative delay of the tubular tissue in acquiring maximal excretory function.

Hare and his collaborators (63) have studied the anatomical development of the renal glomerulus in twenty-nine fetuses and full-term infants. They suggest that the formation of a fine reticulated investment of the glomerular capillaries may be causally related to the increase in glomerular filtration which occurs after birth.

In a companion study to the previous paper, the Hares and their collaborators (64) have studied inulin, urea, mannitol, and hippurate clearances, as well as hippurate Tm, in premature infants. They find the mannitol/inulin clearance ratio to be 0.9 in premature infants. They also find (with a cautionary note

that hippurate at plasma concentrations below 2 mg. per 100 cc. may not be as completely extracted in infants as in adults) the average filtered fraction as calculated from the inulin/hippurate ratio in premature infants to be 0.34, a value much higher than occurs in the adult. Higher values for all of the previously mentioned measurements occur in infants over fifty days of age, but in the same weight range. This suggests that the development of kidney function correlates more closely with postnatal than with gestational age.

Renal Blood Flow

The assessment of any estimation of a discrete renal function is enormously improved if one can relate the discrete renal function to another function of the organism. For instance, one can relate urea clearance to the body surface area; one can relate tubular reabsorption of chloride to the weight of the kidney; and one of the most useful correlations of the physiological function of the kidney is the relation of the discrete function measured to the rate of flow of blood through the kidney. Renal blood flow would be determined with great precision by calculating the renal clearance of a compound, if this compound were completely removed from the blood in a single passage through the kidney, and were excreted quantitatively into the urine (i.e., the compound must not be synthesized nor metabolized by renal tissue, nor must it leave the kidney via lymph or by diffusion to surrounding tissues). For a more complete discussion of this topic, see reference (65). No such compound has as yet been found. However, sodium *p*-aminohippurate is almost completely (*circa* 90 per cent) extracted from plasma by the human kidney; since this hippurate does not enter human erythrocytes its clearance, multiplied by the factor 1.1, approximates renal plasma flow in the normal man, and renal plasma flow divided by 1 minus the hematocrit ratio equals total renal blood flow. In disease and under stress (e.g., hemorrhage) the hippurate clearance may be much lower than normal. In such instances, unless one has access to renal venous blood, it is impossible to ascertain whether the clearance truly mirrors renal blood flow or whether real damage is present, thus depressing the extraction ratio of hippurate appreciably below 0.9. Van Slyke, *et al.* (66) reported that in dogs subjected to shock, if renal ischemia is monetary, there is no decrease in the ability of the kidney to extract hippurate. If ischemia is maintained for twenty minutes

or more there is, upon resumption of an adequate flow of blood through the kidney, a decreased ability to extract hippurate. This situation was also found to prevail in animals whose renal artery had been clamped for varying periods of time (67). A similar depression of the hippurate extraction would occur if comparable renal damage were caused by an infectious or toxic agent.

Thus the use of renal clearance of *p*-aminohippurate to estimate renal blood flow depends upon a normal extraction of hippurate, just as the estimation of glomerular filtration or of any tubular function depends upon a normal ability of the renal tissue to perform these functions. The experimenter who is studying renal function in disease can presume that there has been no kidney damage and, consequently, that the functions measured are representative of the particular experimental condition so long as the renal blood flow estimation based on the hippurate clearance is in the normal range. In man (and these comments will also hold for most experimental animals), if the blood volume and the cardiac output are in the normal range and it is found that the hippurate clearance is decreased, one is faced with three possible situations: (*a*) a normal rate of flow of blood through damaged kidneys whose extraction ratio is decreased; (*b*) a decreased rate of flow of blood through the kidneys by diversion of the normal renal fraction of the cardiac output; or (*c*) a combination of (*a*) and (*b*).

Diversion of renal flow is observed in shock. As pointed out by Van Slyke *et al.* (66, 68) the body, since the kidney has an enormous reserve, will divert blood from the kidney in order to maintain an adequate circulation to the brain, lungs, heart, and perhaps to other organs such as the liver.

The only observation that the writer has found in the literature which might enable one to decide whether a decreased sodium *p*-aminohippurate clearance was due to renal damage or to a shunting of blood from the kidney is contained in the observations of Smith (69). Smith found that the administration of a pyrogen would result in a hyperemia of the renal tissue. Thus, clearances below the expected range should be increased after giving a pyrogen if blood were being diverted from the kidney.

Phillips (70) found that hippurate, creatinine, and urea clearances were frequently low in patients with typhus fever. Since it was known from postmortem studies of renal tissue in this disease that there was often very little microscopic evidence of renal dam-

age and, since observation of the patients in this disease disclosed little sweating while a high fever was maintained over a two- or three-week period, it appeared not unlikely that in some instances the blood was being shunted to the periphery so that the excess heat of the body could be dissipated. In order to determine the amount of renal damage and the amount of shunting of blood from the kidney in these patients, clearances were performed on patients before and after the rapid administration (100 cc. per min.) of from 1,000 to 1,500 cc. of plasma; it was thus possible to compare kidney function before and after the blood volume had been increased approximately 25 per cent. It was found that certain patients did not have any increase in their hippurate, creatinine, or urea clearances after the administration of plasma. Further, since there was no evidence of cardiac embarrassment and since on recovery from typhus fever their clearances came back to the normal range, it was to be presumed that renal damage was responsible for the decreased clearances. In other patients it was found, however, that upon administration of plasma, the hippurate creatinine, and urea clearances immediately returned to the normal level. The only conclusion which could be drawn, consequently, was that before plasma had been administered blood had been shunted from the kidney.

Pai (71) has studied in India the urea clearance in patients without evidence of kidney disease, and he also reports studies made by Gokhale, Srikantia & Shamanna. The result of these observations on a total of 199 patients would indicate that the average urea clearance is in the neighborhood of 35 cc. per min. in individuals living in India, instead of the American average of 54½ cc. a minute. The author concludes that this may be due to the lower protein diet on which the patients in India live or that Indians may have a different normal range for urea clearance than Americans. The writer of this review has made similar observations on patients in Egypt, and it is his impression that a decrease in renal blood flow is probably the more important factor. It is of more benefit to the patient with a high fever, homeostatically, to increase the dissipation of heat through the skin, even though the dissipa- of products excreted by the kidneys is thereby decreased. Patek and co-workers (72) have studied the effect of intravenous serum albumin on renal function in three patients with cirrhosis of the liver. The authors find that immediately after the administration

of 200 cc. of 25 per cent human serum albumin there is an increase of both glomerular filtration and renal plasma flow. They found further that the hippurate clearance was always increased more than was the inulin clearance, thus decreasing the filtered fraction. These authors do not point out that their use of intravenous human albumin affords them a means of determining whether or not the individual can increase his renal blood flow.

Merrill (73) has studied the mechanism of salt excretion in patients with congestive heart failure. In his studies the renal vein was catheterized and the extraction and excretion of *p*-aminohippuric acid and inulin were determined. He found that the extraction ratios of *p*-aminohippurate and inulin were in the normal range. Consequently, since the clearances were low, these patients had a greatly depressed renal blood flow and glomerular filtration. His studies also showed that the reduction in renal blood flow was greater than the reduction in cardiac output, thus indicating renal vasoconstriction.

Eagle & Newman (74) have studied the renal clearances of penicillins F, G, K, and X in rabbits and in man. In man, they find that the clearance of penicillins F, G, and X is approximately the same as that of hippurate. They find that the clearance of penicillin K in man is from one-quarter to one-half that of penicillins F, G, or X.

Selkurt (75) has studied renal blood flow in normal and denervated dog kidneys and related it to effective arterial pressure. His observations would indicate that over a wide range of effective arterial pressure there is very little change in renal blood flow, and further that with a decrease of arterial pressure the decrease in renal blood flow is not proportional and is always much less, on a percentage basis. His experiments also lead him to conclude that glomerular filtration begins in the dog kidney when the renal arterial pressure is about 34 mm. Hg and gradually increases as the arterial pressure increases. These facts suggest that renal blood flow probably persists in the dog even at a lower arterial pressure than 34 mm. Hg. Observations by Batten *et al.* (76) on the relationship between arterial pressure and renal blood flow would tend to support this; they find that, in plotting the renal blood flow against the arterial-venous difference of pressure, all experiments tended to intercept zero renal blood flow at a pressure of approximately 20 mm. Hg. In these experiments they were dealing with

the isolated dog kidney although the experiments were so performed that there was relatively little chance for the kidney to be ischemic at any time during its preparation for use as an isolated kidney.

An important, careful study of the effect of increased intra-abdominal pressure on renal function in man has been made by the Bradleys (77). They have studied renal plasma flow, glomerular filtration rate, and tubular function with saturation techniques in seventeen normal human subjects during and after the application of a pneumatic abdominal girdle, which enabled them to increase the abdominal pressure. Using the venous catheterization technique they found that the application of a pressure of 80 mm. Hg to the abdominal wall effected an increase of intra-abdominal venous pressure of about 20 mm. Hg. Under these conditions, the renal plasma flow and glomerular filtration rate were decreased on an average of about 25 per cent. There was no change in the filtered fraction nor was there a change in the extraction of sodium *p*-aminohippurate by the kidney. These observations indicated that the clearance methods were valid under the conditions of the experiment and further that there was an absence of arterio-venous shunting in these experiments. They believe that the elevation of renal venous pressure was probably sufficient to acccount for the reduction of renal plasma flow.

Herrin (78) concludes from studies on rabbits that the azotemia of experimental intestinal obstruction is due to a decreased renal blood flow. White, Heinbecker & Rolf (79) report that in the hypophysectomized dog renal blood flow, cardiac output, and oxygen consumption are about equally decreased, *circa* 50 per cent of normal.

Glomerular Filtration

The clearance of inulin still continues to be the accepted standard for measurements of glomerular filtration in man just as creatinine is in the dog and lower animals.

Confirming previous studies, Pitts & Lotspeich (80) find that the thiosulfate clearance is a valid measure of glomerular filtration in the dog. These authors further demonstrate that there is no effect on the *p*-aminohippurate clearance when thiosulfate is simultaneously administered; and since thiosulfate, unlike creatinine,

is not a buffer, it is of special value in studying the renal function in acidotic animals. The virtue of thiosulfate over mannitol and inulin, which are also without buffering ability, lies in the simplicity of its analysis.

The clearance of mannitol and its relation to the inulin clearance have been studied recently by many authors and the consensus from the following authors is that the ratio of mannitol to inulin clearance is 0.9: Corcoran & Page (81); Berger, Farber & Earle (82); West, Smith & Chasis (62); Barnett, McNamara, Hare & Hare (64).

Other substances have been reported recently which may estimate glomerular filtration quite accurately. Among those that have been studied is bacitracin, an antibiotic, obtained from *Bacillus subtilis* (83). Preliminary studies in dogs on polyethylene glycols of varying molecular weight indicate that polyethylene glycols of average molecular weights of 400, 1,000, 1,540 and 4,000 gave an average ratio to the simultaneously determined creatinine clearance of 0.99; the ratios of polyethylene glycols of an average molecular weight of 6,000 were consistently and significantly less than one (84). Among other compounds which may be of use is allantoin, reported by Friedman, Byers & Abrahm (85); unfortunately reference clearances (e.g., inulin) were not performed on their patients.

Gukelberger (86 to 91) has studied glomerular filtration in animals and in normal man, using both inulin and creatinine clearances. The latter were performed using his dinitrobenzoic acid method (see section on METHODOLOGY). He has studied the effect of various hormonal preparations and hyperthermia as induced by shortwave radiation. Unfortunately, in his studies there are no determinations simultaneously made to indicate renal blood flow. His most interesting observation is that the endogeneous creatinine clearance is consistently lower than the inulin clearance, averaging about 56 per cent, a finding at variance with most previous studies.

Josephson (92) has studied glomerular filtration, renal plasma flow, and renal tubular mass in normal individuals and in patients with kidney damage of varying degree. Assuming a constant tubular excretion of creatinine, he concludes that in parenchymatous kidney diseases the tubules are always damaged when there is glomerular injury, but that this damage is usually less than that

to the glomeruli. He also reports that treatment of the kidney region of healthy men with short-wave radiation [cf. Gukelberger (89)] resulted in a temporary decrease of diodrast clearance.

In a preliminary article Lotspeich (93) has studied the glomerular filtration in normal, pair-fed, and adrenalectomized rats. The adrenalectomized animals, maintained on sodium chloride, do not have a significantly different glomerular filtration rate than do the normal animals or the pair-fed controls.

Two papers of theoretical interest on the subject of glomerular filtration by Gomez (94, 95) present calculations and formulae for defining hydrostatic pressure, blood flow, and oncotic pressure in the kidney.

Elkinton, Winkler & Danowski (96) have considered the transfers of cell sodium and potassium in experimental and clinical conditions in an article which includes a review and analysis of many of the studies which Winkler and his collaborators have made in this field.

Ekehorn (97 to 102) continues his diatribe against Smith and his collaborators (69). Unfortunately for Ekehorn, while in many instances the dialectics are in his favor, the scientific facts favor Smith, e.g., compare Addendum [(100), p. 136] with Table II [(65), p. 321].

Tubular Activity

Barclay & Kenney (103) discuss previous work which has been done and attempt to devise a satisfactory index for renal tubular reabsorption. They arrive at a formula which enables them to relate this function in different experiments on the same individual; further, they believe that it is possible by their calculations to relate experiments performed on one subject to similar experiments performed on another subject.

Berliner & Kennedy (104) and Mudge, Foulks & Gilman (105) have studied the excretion of potassium in the normal dog. The first authors, basing their observations on simultaneous inulin and creatinine clearances, and the second authors, basing their studies on thiosulphate and creatinine clearances, have found that in dogs it is possible to obtain an excretion of potassium which is greater than the possible amount of potassium which can be filtered in the period of time studied. The authors point out that previous stud-

ies have been done which would indicate that this was likely, but the absence of careful simultaneous studies of glomerular filtration rendered this interpretation theoretical. It is not impossible that if similar careful studies are done with other substances, supposedly excreted only by filtration, conditions may be found in which there will be evidence of their excretion by the tubules.

Pitts and his collaborators have continued to study the renal regulation of acid-base balance. In their first paper (106) they repeat experiments, performed previously on the dog, on four healthy human subjects. The observations and conclusions which they reach are identical with their previous conclusions in the dog experiments, i.e., that acid must have been added by some mechanism of active transport resident in the renal tubular cells to the filtrate as it passed along the nephron. They suggest that this addition of acid is effected by the exchange of hydrogen ions, formed within the tubular cells, for ions of fixed base in the tubular urine; and they believe that carbonic acid is the most likely source of intracellular hydrogen ions. The writer of this review is in full accord with the authors' primary conclusion, which they emphasize: to wit, that their experiments justify the use of the dog for analysis of problems of acid-base regulation, and that conclusions drawn from such experiments on the dog can also be applied to man.

In a second paper these same authors (107) studied the factors which control the excretion of titratable acid in man. Again, the experiments are similar to previously reported experiments on the dog. In man they find that the kidneys react as though the normal range of plasma bicarbonate (24 to 26 mM per l.) is a state of mild acidosis and, when the plasma bicarbonate is reduced to 20 mM per l., a maximum stimulus is applied to the acid-excretory mechanism. In another paper Pitts and his collaborators (108) studied the reabsorption and excretion of bicarbonate in normal man. The experimental data, they say, is in accord with the prediction that the partial pressure of carbon dioxide in the urine increases in proportion to the rate of reabsorption of bicarbonate in the distal tubules; also the rate of excretion of titratable buffer acids is related inversely to the rate of reabsorption of bicarbonate in the distal tubules. Further studies on acidosis from the same laboratory are presented by Sartorius, Roemmelt & Pitts (109), who studied alterations in the renal function of normal human subjects resulting from experi-

mental metabolic acidosis. Jahan & Pitts (110) find parathormone to be without effect on the renal tubular reabsorption of inorganic phosphate.

Wolf (111) presents experiments which, he says, confirm or favor the hypothesis of Briggs: renal ammonia excretion has nothing to do with the regulation of the acid-base balance of the body. This concept is based on the fact that following the production of an acidosis, there is a long lag before ammonia excretion builds up to a value which is sufficient to enter into the base-economy; further, when the acidosis is treated, there is a lag in cessation of ammonia excretion. However, it is not impossible that dehydration, the availability of glutamine, or other factors limit the rate of ammonia excretion. While experiments have never been performed in which maximal acidosis for any one animal has been produced in a short period of time (judged by the maximal rate of ammonia excretion), this does not mean that it is impossible to do so. Phillips (112) and Winkler (113) independently attempted to ingest 15 to 20 gm. of ammonium chloride in suitable quantities of water after evoking a water diuresis. They planned to study ammonia excretion subsequently but their attempts were frustrated by projectile vomiting.

Van Slyke (114) has carefully analyzed data which has enabled him to compare various formulae for calculating the excretion of urea as it is effected by urine volume. He concludes that the original formula of Moller, McIntosh & Van Slyke is quite adequate for ordinary purposes and the more recent formula of Dole (115) fits the experimental data best; the recent formulae proposed by Bing (116) and by Williams (117) proved less accurate when used to cover the maximal variations in rate of urine excretion in man. Van Slyke also points out that it may be possible, by observing the effect of urine volume on urea clearance in patients who have damaged kidneys, to estimate the optimal rate of urine excretion for optimal urea dissipation. While urea is not the factor responsible for the toxic effects of uremia, still it is not unlikely that if one can evoke optimal urea excretion, he may also obtain optimal excretion of the substances (potassium, etc.) which are responsible.

Wright *et al.* (118) continue their studies on the renal clearance of arginine, histidine, lysine, and methionine. The renal reabsorption of methionine in normal dogs is also studied by Ferguson,

Eaton & Ashman (119). Eiler, Althausen & Stockholm (120) have studied the absorption of galactose by the renal tubules in a dog. A comprehensive study of ascorbic acid excretion by the human kidney, particularly with reference to the mechanism of its renal reabsorption, is reported by Ahlborg (121).

Friedman (122) has studied the excretion of uric acid, both in rat and in man, following administration of glycine. Drawing an analogy to the conclusions of Pitts (123), who studied the effect of glycine upon the reabsorption of creatinine, Friedman suggests the probability that glycine increases the excretion of uric acid by impeding the renal tubular reabsorption of uric acid filtered by the glomerulus.

The reabsorption, by the tubules, and excretion of sodium and chloride have been studied by the following authors: Roemmelt, Sartorius & Pitts (124); Cizek & Holmes (125); Wesson, Anslow & Smith (126); Mokotoff, Ross & Leiter (127); and Lotspeich, Swan & Pitts (128).

Redish and associates (129) observed early in the post-anuric stage in a patient recovering from sulfathiazole poisoning that the Tm_{PAH} had a negative value, thus indicating tubular back-diffusion of *p*-aminohippurate (PAH). Phillips & Hamilton (67) discuss this aspect of tubular reabsorption. Shapiro (130) discusses the site of action of phlorizin on tubular mechanisms.

Experimental Induction of Renal Damage

Morehead & Little (131) have reported a study of twenty-eight mongrel dogs in which they find that chronic interstitial nephritis is present in more than half of the fully grown animals. These observations confirm those of Bloom (132), who found in a study of two hundred dogs, that one hundred eight showed focal interstitial nephritis. The importance, of course, of these observations lies in the fact that unless care is taken in controlling the experiment, the mere finding of renal damage after an injection of an agent does not mean that the agent has caused this damage. This difficulty is obviated if the experiments include studies of clearances of different compounds before and after the supposedly damaging agent has been given, or if serial biopsies are used as did Glynn (133), who studied the effect of staphylococcus toxin on the kidney. Not only is Glynn's method of preparation detailed, but he also points out how important it is to select one's animals

very carefully before giving the damaging agent. Some animals he found to be susceptible while other animals were not susceptible to the agent.

Simonds, Linn & Lange (134) review the general subject of the production of experimental glomerulonephritis. An extensive review of the literature is contained and suggestions and comments are made as to the use of various agents for producing glomerular damage.

The prolonged administration of vitamin B has again been implicated in causing renal damage by Freeman, Rhoads & Yeager (135). Their observations confirm those of Danowski, Winkler & Peters (136). Lowenhaupt & Greenberg (137) find that rats on a chloride-deficient diet develop a renal lesion. Baxter & Ashworth (138) find in patients with portal cirrhosis that degenerative changes of the convoluted loops and, to a lesser extent, of the loops of Henle are found in all individuals. Fishman & Govier (139) find that rats on a stock diet or on a vitamin B-deficient diet develop profound necrotizing lesions in the kidney when DL-serine is given orally. They also noted a marked decrease in the cocarboxylase content of the kidney, the decrease being directly related to the extent of the necrotizing lesions of the tubules.

Freeman (140) corrects his previous conclusions (141) reported by Dock (142) in his review of the kidney, concluding that oxalate, rather than plasmaphoresis, was apparently responsible for the renal damage in his experiments, for when heparin was used instead of oxalate no renal damage resulted.

Cuthbertson & Greenberg (143) placed rats on a diet containing only 2 to 5 mg. per cent of chloride with 2 per cent carbonate and bicarbonate replacing the usual concentration of chloride. Pair-fed control animals were also studied and it was found in the animals on the chloride-deficient and high-bicarbonate diet that extensive renal damage occurred; not only were the tubules damaged but the glomeruli were also involved. They point out that Addis, MacKay & MacKay (144) kept rats on a high sodium bicarbonate diet for three hundred days with no resulting kidney pathology, hence the chloride deficiency, rather than the alkalosis, is more likely responsible for the renal damage.

Hay & Seguin (145) report studies on the nephrosclerosing effect of anterior pituitary preparations. They also compare other

organ extracts and find, that under the conditions of their experiments, only the anterior pituitary preparations were effective; lyophilization rendered their anterior pituitary preparation ineffective. Menten & Janouch (146) studied the renal damage which occurred following alloxan administration and report that there is an associated marked decrease in the alkaline phosphatase content of the kidney. Morehead, Fishman & Artom (147), in further studies on the nephrotoxic action of DL-serine, find that the supplementation of the diet by choline hydrochloride, cystine, glycine, and B-vitamins did not alter the effect of DL-serine.

The Caveltis (148, 149, 150) report the production of glomerulonephritis by means of the injection of autoantibodies. The incidence of renal lesions is about 50 per cent in experiments performed on rabbits and rats. It is to be hoped that measurements of glomerular and tubular function will be made in future studies by these authors. Gukelberger and his collaborators (151, 152, 153) have compared the renal damage produced by the Masugi method (which consists of injecting renal antibodies into the experimental animals) and by injecting mercuric chloride. The physiological studies reported include the clearances of water, phosphorus, urea, and inulin. They also studied the histological picture and it would appear that with both agents effecting renal damage there is very little difference except for the time factor; six hours following injection of mercuric chloride the histological picture is comparable to that which occurs four to six days after the antibodies have been given.

Pressman & Keighley (154) have reported observations in which they combine antirat-kidney serum with radioactive iodine. In their experiments they find that the autoantigen is located, after it has caused kidney damage, primarily in renal tissue.

Marvel *et al.* (155) have reported on the structure of urea-formaldehyde resins. It is possible that the combination of urea and formaldehyde, or derivatives of the same or similar compounds, might be the cause of casts which occur in the tubules under certain circumstances.

Perlstein and co-workers (156) report studies on the administration of large amounts of penicillin to rabbits (equivalent to giving a seventy-kilo man fourteen million units of penicillin). Under these circumstances, anuria developed and it is presumed

that the penicillin was responsible for the renal damage which occurred.

Treatment of Renal Damage

Abbott & Shea (157) report their experimental observations on the treatment of renal damage by peritoneal lavage in dogs. It would appear that their observations were performed at about the same time as was the work of Fine, Frank & Seligman (158), who have demonstrated its value in man. Reid, Penfold & Jones (159) report a case in which they treat acute renal damage by renal decapsulation and peritoneal dialysis.

A clinical and pathological study of the kidney in patients who have died following thermal burns is made by Goodpaster, and associates (160). The authors conclude that while most of their patients with renal dysfunction died of causes other than renal failure it is believed that if these complications had been avoided the patients would have gone on to death from renal failure. Thus, they concur in the observations made by Van Slyke *et al.* (66).

Lethal Renal Ischemia

Previous to 1943 there were no quantitative observations in the literature on the duration of time required to produce irreversible damage following occlusion of both renal arteries or removal of one kidney and occlusion of the remaining renal artery.

Scarff & Keele (161), confirmed recently by Badenoch & Darmady (162), found that in rabbits with one kidney removed and a clamp applied to the whole remaining renal pedicle it was necessary to obstruct the renal circulation for sixty to one hundred twenty minutes in order to produce sufficient damage so that the animal would not recover. Renal ischemia for ninety minutes was fatal in one of two animals; of three animals who had the renal clamp applied for one hundred twenty minutes one recovered, while one animal who had the clamp applied for one hundred five minutes recovered.

Hamilton, Phillips & Hiller (163) have reported in detail from experiments cited by Van Slyke *et al.* (66) that in winter months when environmental temperature was low, dogs could withstand, following the removal of one kidney, three hours of renal ischemia resulting from obliteration of the lumen of the remaining renal artery; of six dogs subjected to renal ischemia for four hours, three

died while three lived for over a month before sacrifice. However, they found that in the summer months, when the environmental temperature ranged from 30° to 40°C., half of the animals died when renal ischemia had been maintained for only three hours; thus indicating that at the higher environmental temperature the restoration or regeneration of renal tissue was not rapid enough to prevent accumulation of metabolic products which were eventually lethal.

Koletsky & Gustafson (164) have performed similar experiments on rats. They find that rats readily survive a thirty-minute period of complete renal ischemia and usually survive a one-hour period. The mortality at ninety minutes of renal ischemia was 73 per cent and at two hours the procedure was uniformly fatal. The findings were to be expected since the rat has a much higher metabolic rate than does the dog and, in consequence, it would be expected that metabolic products might pile up more rapidly than the rats could regenerate renal tissue.

Reaves (165) has reported two patients who were inadvertently subjected to bilateral ligation of the ureters. In one patient the ureters were obstructed for thirty-six hours and upon relieving the obstructions the patient recovered. In the other patient the ureters were ligated for over seventy-two hours and the patient did not recover.

The importance of ascertaining the length of time which is required for a complete ischemia to be lethal should be obvious. Further, the duration of time which is required before the animal dies is equally important. Dogs with both kidneys removed will die in from four to eight days, if no supporting therapy is provided, according to a report by Hamilton, Phillips & Hiller (163). Thus it would appear obvious that if a dog has been subjected to a procedure which results in renal damage and the dog then dies on the third day, renal damage alone cannot have caused the death; damage must have been incurred in other areas of the body.

Limitation of space prevents discussion of recent articles on the crush syndrome. The readers are referred to the review article in this subject published by Corcoran & Page (166).

Hemoglobin—Foe or Savior

Hematuria, occurring in blackwater fever, mismatched transfusions, etc., has directed attention to the kidneys and in those pa-

tients who have died casts containing hemoglobin (or its derivatives) have been found in the kidneys. Further studies of such patients also revealed clinical evidence of renal damage. In consequence, it was suggested that the presence of hemoglobin in the plasma, either as the result of its intravenous administration or as a result of laking of erythrocytes, effected renal damage. The majority of the earlier studies on this subject were devoted to finding out the mechanism of the renal damage which frequently accompanied hematuria. However, it gradually became evident that the situation was not a simple one and studies in this field can now be divided into two schools. One has devoted its attention (particularly since reporting of the crush syndrome) to devising experiments which produce renal damage after hemoglobin and/or its derivatives have been injected; usually the animals have been treated previously by dehydration, acidosis, various dietary restrictions, etc.

The other has been primarily interested in utilizing hemoglobin as a blood substitute, stems from Amberson's original observations (167), and was prosecuted during the war by the laboratories of Lamson and Van Slyke. This school, realizing that hemoglobin would be a very effective blood substitute if it has no damaging effect on the kidneys or other tissues, places all its emphasis on preparing hemoglobin in such a fashion that it will not be toxic; it then attempts to find out if the individual, man or animal, after subjection to reasonable stress will still tolerate the hemoglobin administered intravenously.

It should be pointed out that in this field one is frequently confronted with deductions which do not take into account the faulty care the patient has received. For instance, Dardinski (168) reports pathological studies on a patient who was Rh negative, who developed anuria after two transfusions with Rh positive blood, and subsequently died. The postmortem studies demonstrated that there was not sufficient pathology to account for the patient's anuria on the basis of tubular blockage. This patient, in the fourteen-day period before death, excreted 805 cc. of urine while receiving a total of 39,485 cc. of fluid by mouth, subcutaneously and intravenously! The notation is made that the patient had a marked anasarca; further, the blood nonprotein nitrogen was only 161 mg. per 100 cc. hence it would appear that if the patient had not been given such

enormous amounts of fluid, he would have been able to survive the renal damage which had occurred. Unfortunately, patients such as this are usually (*N. B.* not in this instance) cited in the literature as furnishing evidence that laking of cells or the presence of hemoglobin in the plasma and its excretion by the kidney resulted in kidney damage with death in uremia.

Maegraith (169) has a review article on the anuria which occurs in blackwater fever. The present most widely held theory is that in blackwater fever (which is an occasional complication of malaria) there is disruption of red cells with liberation of hemoglobin, the hemoglobin is filtered by the glomerulus, and in the presence of acid urine, hemoglobin (or derivatives) is precipitated in the tubular lumen causing renal damage. The author points out several discrepancies in this theory and in the current methods of treatment. In regard to the use of alkali in the treatment, he points out that Palmer & Van Slyke in 1917 (170) found that normal individuals excreting acid urine or urine which is neutral will, following the administration of small amounts of sodium bicarbonate, excrete urine which is alkaline; however, they found that in patients who had renal damage the urine may remain acid in spite of excessive alkali therapy. Hence, the suggestion that large amounts of alkali should be given when there has been intravascular haemolysis and kidney damage is most unwarranted, and Maegraith (169) cites clinical evidence that renal damage is more frequent in blackwater fever patients who have been given alkali. He also discusses the sodium chloride content of the urine and reports on a series of studies by Ross (171), who found that in patients who have renal damage in blackwater fever there is a greatly decreased excretion of sodium chloride. Consequently, the observations of Baker & Dodds (172) that hemoglobin is only precipitated in the urine, when the chloride content is elevated, is not applicable here. Further, he points out that very frequently in oliguric cases the urine during the recovery period contains practically no casts nor evidence of hemoglobin; this would seem to indicate that there had not been plugging of the lumen of tubules by hemoglobin.

In a subsequent paper, Maegraith, Havard & Parsons (173) discuss renal damage which is found in a wide variety of conditions, including blackwater fever, incompatible blood transfusion, crush syndrome, sulphonamide poisons, icterus neonatorum, alkalosis of

of gastric tetany, prerenal-azotaemia, septic abortion, concealed accidental hemorrhage, yellow fever, cholera, diabetes, hepatorenal syndrome, etc., and conclude that the common factor in these cases is shock. Their subsequent reasoning is not particularly sound and it would appear that they believe it is possible that toxic products arise in some of these instances because blood has been cut off from an extremity or organ and some metabolic process is interfered with; in consequence, toxic products resulting from lack of oxygen are carried to the kidney and produce the damage.

To the reviewer it is much more likely and logical, in instances in which the individual was in shock at the time the mismatched blood was given (or the erythrocyte laking occurred), that the renal damage, due to a greatly decreased flow of blood through the kidney, had already occurred. As a result of the transfusion (even though mismatched blood was used), adequate blood now flows through all vessels and the individual's life is saved but he does have renal damage of a greater or lesser degree. It is true that in those individuals who die the kidney will contain hemoglobin casts but this does not necessarily mean there was any renal damage due to the hemoglobin itself (67). While it has been impossible to reproduce the crush syndrome in experimental animals, still it may be that the experimental animals used are not so susceptible to renal ischemia as is man. This suggestion has been put forward by Van Slyke and his collaborators (65).

While it is not to be doubted that hemoglobin or its products when infused under the certain conditions into animals will produce renal lesions, much greater care must be used than has been used in the past in preparing hemoglobin solutions and in devising the experimental conditions before concluding that hemoglobin and/or its products per se are nephrotoxins.

Simonds, Linn & Lange (134) have pointed out the nephrotoxic action of staphylococcus toxins and toxins from other organisms. Hence, in the preparation of hemoglobin solution, an excellent culture medium, one must not only maintain sterile precautions at all times but must take cultures at key points; further, the solution must be tested for pyrogens and toxicity before it is finally used. It should be obvious that the use of organic solvents for laking the cells is open to criticism. It is surprising in how few experiments adequate precautions of the type just mentioned have been taken.

The literature on hemoglobinuria up to 1942 has been reviewed by Yuile (174). He and his collaborators have reported their method for preparing hemoglobin by laking the erythrocytes with ether (175) and have studied the tubular reabsorption of hemoglobin (176). Yuile, Gold & Hinds (177) conclude "hemoglobinemia *per se* is in all probability not the basic factor in the production of the renal lesions seen in . . . blackwater fever, crush syndrome, transfusion reactions, etc." They present experiments which would indicate that their preparation of hemoglobin does produce further renal damage when injected intravenously into rabbits rendered acidotic whose kidneys were acutely damaged by (*a*) clamping the renal pedicle for twenty-five minutes, or (*b*) administering sodium acid tartrate. Black (178) appears to subscribe to the theory that hemoglobin excretion by the kidney does not cause renal damage.

Lalich (179) has reported studies on the effect of homologous hemoglobin on the kidneys of normal and dehydrated animals. While it is true that in his experiments three animals died after dehydration and injections of hemoglobin, at the same time three other animals in the experiment died who did not have an elevation of blood urea at the time of death.

Lalich in a further paper (180) finds that in rabbits it is possible to produce a hemoglobinuric nephrosis; five of his fifteen animals died. In these studies he reports that focal necrosis of the liver and pulmonary edema were present in some of the animals which died. Evidently the lesion then is not limited solely to the kidney. In this paper the author has altered his original method of preparing hemoglobin by adding ether equivalent to 1 per cent of the total volume of water and centrifuged erythrocytes. No note of the sterility of the solutions used was made, nor is there any indication that the studies which he made on the alteration of the hemoglobin showed any alteration. The hemoglobin given was equivalent to 1.8 gm. per kg., divided into nine to ten intravenous doses over a three-day period. This dosage compares with 33 gm. per kg. given to rats by Rather (181).

Harrison *et al.* (182) likewise studied the effect of hemoglobin on dogs. They found that hemoglobin could be given with apparent inpunity so long as there was a normal rate of urine excretion. However, in the presence of marked dehydration hemoglobin and methemoglobin were toxic.

Flink (183) has studied the renal damage which he has been able to produce by the injection of hemoglobin into dogs. Two methods of preparing hemoglobin were used. Ten animals were studied and only two of the animals developed renal damage of a severe enough degree to cause death. From the paper it is impossible to say whether the two animals that received hemoglobin and died had received solutions which were known to be sterile. Although cultures were taken and the blood may have been sterile at that time, it was often kept for several days before being infused. Further, it is of interest that while the animals died with over 200 mg. of urea nitrogen per 100 cc. of blood both animals at the time of death still had a urine volume output which was in the normal range.

Corcoran & Page (184), from studies which they have made on hemoglobin and its derivatives, conclude that myoglobin and hematin administered to aciduric conscious dogs cause varying degrees of renal functional impairment.

Investigators, who prefer to look upon hemoglobin as a savior rather than a foe, have devoted their attention to improving the method of preparation of hemoglobin solutions and to ascertaining under what conditions hemoglobin should not be given to the individual.

Amberson and co-workers (185) report their observations in giving hemoglobin to human patients. Amberson's earlier study on the administration of hemoglobin solutions to animals (186) is, of course, classic.

O'Shaughnessy *et al.* (187) have reported the administration of hemoglobin solutions to four patients. However, the solutions used were not particularly satisfactory since they were following a preparation which Amberson described in 1937 (186).

Hueper (188) injected a hemoglobin preparation of Pfanstiehl, 2 per cent in saline, into three dogs. He found no evidence of kidney damage in any of the animals. The animals were given a total of 28 gm. each over a period of five weeks.

Lamson, during the war, became very interested in the possibility of the use of hemoglobin as a blood substitute and observations performed in his laboratory are reported by Lamson, Robbins & Grieg (189).

Hamilton *et al.* (190) have described in detail their procedure for the preparation of sterile nonpyrogenic solutions of oxyhemo-

globin which have the approximate protein content and electrolyte composition of plasma. They find there is no conversion of hemoglobin to methemoglobin when the solutions are stored at 4°C. for a short period of time. However, over a period of eighteen months there is an appreciable conversion of hemoglobin to methemoglobin.

Farr, Hiller & Van Slyke (191) have described a method for preparing dried hemoglobin without loss of activity. The technique is quite laborious and an improved method of preparing a lyophilized hemoglobin preparation has been reported by Pennel & Smith (192).

Hamilton, Hiller & Van Slyke (193) have studied the effect of intravenous administration of hemoglobin solutions on dogs in hemorrhagic shock. From their studies they find that animals who were bled 50 cc. per kg. body weight and in whom the blood volume was replaced by hemoglobin in some instances showed evidence of kidney damage. This is indicated by the elevation of the blood urea and also by the prolonged decrease in urea clearance. This occurred only in animals which were in acidosis and it is of interest that the highest blood urea nitrogen quoted was forty-four. It is certainly not a significant damage and the urea clearances returned to the normal level over the period of a few weeks.

Rather (181) has used hemoglobin solutions prepared following the method of Hamilton and associates (190) in studies done on rats. While he was primarily interested in the athrocytosis which occurs following the intraperitoneal injection of hemoglobin, it is of interest that his animals received 33 gm. of hemoglobin per kilo body weight, a far greater amount than has been given in most of the other studies reported in the literature, and the ultimate effect on the kidneys was slight.

Phillips (194) has administered homologous hemoglobin in a 7 per cent solution, prepared by Sharp & Dohme according to the technique of Hamilton *et al.* (190), to over 30 patients. The solution was administered rapidly (80 to 100 cc. per min.) as would be the case in treating patients in shock. Two patients received 500 cc.; eighteen received 1,000 cc.; eleven received a liter on two occasions; one received 2,500 cc. in unit administrations of 500, 1,000, and 1,000 cc.; and one patient received a liter on each of three separate occasions.

Patients who received more than a single injection received their second and third injections at intervals varying from a week to a month after the initial administration. Urea clearance studies performed on the patients before, during, and after the hemoglobin administration revealed that in most instances there was no evidence of renal damage and in no instance was there irreversible damage.

The evidence that hemoglobin can be prepared in a stable form and infused without necessarily evoking serious renal damage is thus seen to be accumulating.

LITERATURE CITED

1. SCHWEIGERT, B. S., *Proc. Soc. Exptl. Biol. Med.*, **66**, 315–19 (1947)
2. LEMBERG, R., AND CALLAGHAN, J. P., *Australian J. Exptl. Biol. Med. Sci.*, **23**, 1–5 (1945)
3. LEMBERG, R., AND CALLAGHAN, J. P., *Australian J. Exptl. Biol. Med. Sci.*, **23**, 6–12 (1945)
4. LEMBERG, R., AND CALLAGHAN, J. P., *Australian J. Exptl. Biol. Med. Sci.*, **23**, 13–20 (1945)
5. ELLINGER, P., AND COULSON, R. A., *Biochem. J.*, **38**, 265–70 (1944)
6. EULER, U. S., v., *Nature*, **154**, 17 (1944)
7. EULER, U. S. v., *Acta Pharmacol. Toxicol.*, **1**, 29–59 (1945)
8. MICHELSEN, O., CONDIFF, H., AND KEYS, A., *J. Biol. Chem.*, **160**, 361–70 (1945)
9. ADDIS, T., BARRETT, E., AND MENZIES, J. T., *J. Clin. Invest.*, **26**, 879–82 (1947)
10. GUKELBERGER, M., AND WYSS, F., *Z. ges. exptl. Med.*, **3**, 352–59 (1942)
11. PETERS, J. H., *J. Biol. Chem.*, **146**, 179 (1942)
12. BONSNES, R. W., AND TAUSSKY, H. H., *J. Biol. Chem.*, **158**, 581–91 (1945)
13. PHILLIPS, R. A., in *Peters & Van Slyke Methods*, 604B (Williams & Wilkins, Baltimore, Maryland, 1942)
14. HAMILTON, P. B., in *Peters & Van Slyke Methods*, 599 (Williams & Wilkins, Baltimore, Maryland, 1942)
15. ELKINTON, J. R., *J. Clin. Invest.*, **26**, 1088–97 (1947)
16. BARKER, H. G., AND CLARK, J. K., *Proc. Soc. Exptl. Biol. Med.*, **64**, 120 (1947)
17. LANDOWNE, M., AND ALVING, A. S., *J. Lab. Clin. Med.*, **32**, 931–42 (1947)
18. DOMINGUEZ, R., CORCORAN, A. C., AND PAGE, I. H., *J. Lab. Clin. Med.*, **32**, 1192–1202 (1947)
19. DEICHMANN, W., AND THOMAS, G., *Journal Ind. Hyg. Toxicol.*, **25**, 286–92 (1943)
20. DEICHMANN, W. B., AND DIERKER, M., *J. Biol. Chem.*, **163**, 753–60 (1946)
21. DEICHMANN, W. B., AND WITHERUP, S., *Arch. Biochem.*, **7**, 401–8 (1945)
22. DEICHMANN, W. B., KITZMILLER, K. V., AND WITHERUP, S., *Arch. Biochem.*, **7**, 409–13 (1945)
23. DEICHMANN, W. B., KITZMILLER, K. V., DIERKER, M., AND WITHERUP, S., *Journal Ind. Hyg. Toxicol.*, **29**, 1–13 (1947)
24. KRUHØFFER, P., *Acta Physiol. Scand.*, **11**, 16–36 (1946)
25. KRUHØFFER, P., *Acta Physiol. Scand.*, **11**, 37–47 (1946)
26. ENGEL, F. L., PENTZ, E. I., AND ENGEL, M. G., *J. Biol. Chem.*, **174**, 99–105 (1948)
27. COLLINGS, W. D., MARTIN, C. J., AND WALTERS, G. R., *Federation Proc.*, **7**, 22 (1948)
28. LAMSON, P. D., AND DE TURK, W. E., *J. Pharmacol. Exptl. Therap.*, **83**, 250–52 (1945)
29. KEITH, N. M., AND OSTERBERG, A. E., *J. Clin. Invest.*, **26**, 773–83 (1947)
30. MENTEN, M. L., JUNGE, J., AND GREEN, M. H., *J. Biol. Chem.*, **153**, 471–77 (1944)

31. GUNTON, R., AND BURTON, A. C., *J. Clin. Invest.*, **26,** 892–98 (1947)
32. DITTEBRANDT, M., TENNEY, M., AND WEST, E. S., *J. Biol. Chem.*, **152,** 395–400 (1944)
33. EGGLESTON, N. M., JOHNSTON, B. J., AND DOBRINER, K., *Endocrinology*, **38,** 197–211 (1946)
34. MCKITTRICK, D. S., AND SCHMIDT, C.L.A., *Arch. Biochemistry*, **6,** 411–17 (1945)
35. ARCHIBALD, R. M., *J. Biol. Chem.*, **157,** 507 (1945)
36. KINSEY, V. E., AND ROBISON, P., *J. Biol. Chem.*, **162,** 325–31 (1946)
37. MACKENZIE, C. G., AND DU VIGNEAUD, V., *J. Biol. Chem.*, **172,** 353–54 (1948)
38. RUEHRWEIN, R. A., AND HUFFMAN, H. M., *J. Am. Chem. Soc.*, **68,** 1759–61 (1946)
39. BUCHANAN, O. H., BLOCK, W. D., AND CHRISTMAN, A. A., *J. Biol. Chem.*, **157,** 181–87 (1945)
40. WOLFSON, W. Q., LEVINE, R., AND TINSLEY, M., *J. Clin. Invest.*, **26,** 991–94 (1947)
41. WOLFSON, W. Q., AND LEVINE, R., *Federation Proc.*, **7,** 136–37 (1948)
42. KHALIL, F., *J. Biol. Chem.*, **172,** 101–3 (1948)
43. KHALIL, F., *J. Biol. Chem.*, **172,** 105–6 (1948)
44. DE MUYLDER, C., *Arch biol.* (*Liège*), **56,** 1–70 (1945)
45. KUBICEK, W. G., HARVEY, R. B., AND KOTTKE, F. J., *Federation Proc.*, **7,** 68 (1948)
46. KRISS, J. P., FUTCHER, P. H., AND GOLDMAN, M. L., *Federation Proc.*, **7,** 68 (1948)
47. TRUETA, J., BARCLAY, A. E., DANIEL, P., FRANKLIN, K. J., AND PRICHARD, M. M. L., *Lancet*, **II,** 237 (1946)
48. VAN SLYKE, D. D., *Ann. N. Y. Acad. Sci.*, **49,** 593–604 (1948)
49. REUBI, F. C., SCHROEDER, H. A., AND WILLIAMS, A. H., *Federation Proc.*, **7,** 101 (1948)
50. LUCKÉ, B., *Military Surgeon*, **99,** 371–76 (1946)
51. BARRETT, E., AND ADDIS, T., *J. Clin. Invest.*, **26,** 875–78 (1947)
52. ADDIS, T., BARRETT, E., POO, L. J., AND YUEN, D. W., *J. Clin. Invest.*, **26,** 869–74 (1947)
53. BARCLAY, J. A., COOKE, W. T., KENNEY, R. A., AND NUTT, M. E., *Am. J. Physiol.* **148,** 327–37 (1947)
54. WHITE, H. L., AND ROLF, D., *Federation Proc.*, **7,** 133 (1948)
55. TALSO, P. J., CROSLEY, A. P., JR., AND CLARKE, R. W., *Federation Proc.*, **7,** 122 (1948)
56. DRURY, D. R., HENRY, J. P., AND GOODMAN, J., *J. Clin. Invest.*, **26,** 945–51 (1947)
57. MCCANCE, R. A., *Schweiz. med. Wochschr.*, No. 37/38, 857 (1946)
58. CUTTING, M., AND MCCANCE, R. A., *J. Physiol.* (*London*), **104,** 288–98 (1946)
59. CUTTING, M., AND MCCANCE, R. A., *J. Physiol.* (*London*), **105,** 205–14 (1946)
60. WILLIAMSON, R. C., AND HIATT, E. P., *Proc. Soc. Exptl. Biol. Med.*, **66,** 554–57 (1947)
61. HELLER, H., *J. Physiol.* (*London*), **102,** 429–40 (1944)
62. WEST, J. R., SMITH, H. W., AND CHASIS, H., *J. Pediat.*, **32,** 10–18 (1948)

63. HARE, K., UNGEWITTER, L., BARNETT, H. L., AND MCNAMARA, H., *Federation Proc.*, **7**, 51 (1948)
64. BARNETT, H. L., MCNAMARA, H., HARE, R. S., AND HARE, K., *Federation Proc.*, **7**, 5–6 (1948)
65. PHILLIPS, R. A., DOLE, V. P., HAMILTON, P. B., EMERSON, K., JR., ARCHIBALD, R. M., AND VAN SLYKE, D. D., *Am. J. Physiol.*, **145**, 314–36 (1946)
66. VAN SLYKE, D. D., PHILLIPS, R. A., HAMILTON, P. B., ARCHIBALD, R. M., DOLE, V. P., AND EMERSON, K., JR., *Trans. Assoc. Am. Physicians*, **58**, 119–28 (1944)
67. PHILLIPS, R. A., AND HAMILTON, P. B., *Am. J. Physiol.*, **152**, 523–30 (1948)
68. VAN SLYKE, D. D., *Ann. N. Y. Acad. Sci.*, **49**, 593–604 (1948)
69. SMITH, H. W., *Lectures on the Kidney*, 55 (Univ. Ext. Div., Univ. of Kansas, Lawrence, Kansas, 1943)
70. PHILLIPS, R. A. (Unpublished data)
71. PAI, M. L., *Indian J. Med. Research*, **33**, 259–63 (1945)
72. PATEK, A. J., JR., MANKIN, H., COLCHER, H., LOWELL, A., AND EARLE, D. P., JR., *J. Clin. Invest.*, **27**, 135–44 (1948)
73. MERRILL, A. J., *Proc. Am. Federation Clin. Research*, **2**, 8–9 (1945)
74. EAGLE, H., AND NEWMAN, E., *J. Clin. Invest.* **26**, 903–18 (1947)
75. SELKURT, E. E., *Am. J. Physiol.*, **147**, 537–49 (1946)
76. BATTEN, W., OGLE, B. C., RAPELA, C., HEGE, J. R., JR., LITTLE, J. M., AND GREEN, H. D., *Federation Proc.*, **7**, 6 (1948)
77. BRADLEY, S. E., AND BRADLEY, G. P., *J. Clin. Invest.*, **26**, 1010–22 (1947)
78. HERRIN, R. C., *Am. J. Physiol.*, **149**, 494–501 (1947)
79. WHITE, H. L., HEINBECKER, P., AND ROLF, D., *Am. J. Physiol.*, **149**, 404–17 (1947)
80. PITTS, R. F., AND LOTSPEICH, W. D., *Proc. Soc. Exptl. Biol. Med.*, **64**, 224–27 (1947)
81. CORCORAN, A. C., AND PAGE, I. H., *J. Biol. Chem.*, **170**, 165–71 (1947)
82. BERGER, E. Y., FARBER, S. J., AND EARLE, D. P., JR., *Proc. Soc. Exptl. Biol. Med.*, **66**, 62–66 (1947)
83. EAGLE, H., NEWMAN, E. V., GREIF, R., BURKHOLDER, T. M., AND GOODMAN, S. C., *J. Clin. Invest.*, **26**, 919–28 (1947)
84. SHAFFER, C. B., CRITCHFIELD, F. H., AND CARPENTER, C. P., *Federation Proc.*, **7**, 111 (1948)
85. FRIEDMAN, M., BYERS, S. O., AND ABRAHM, P. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 522–23 (1947)
86. GUKELBERGER, M., AND BELLAC, F. J., *Z. ges. exptl. Med.*, **111**, 405–10 (1942)
87. GUKELBERGER, M., *Deut. Arch. klin. Med.*, **189**, 436–501 (1942)
88. GUKELBERGER, M., *Helv. Med. Acta*, **10**, 47–49 (1943)
89. GUKELBERGER, M., *Helv. Med. Acta*, **12**, 175–88 (1945)
90. GUKELBERGER, M., *Helv. Med. Acta*, **12**, 529–38 (1945)
91. GUKELBERGER, M., *Arztliche Monatsh.*, **3**, 305–56 (1947)
92. JOSEPHSON, B., *Sartryck Nord. Med.*, 1–16 (1945)
93. LOTSPEICH, W. D., *Federation Proc.*, **7**, 74 (1948)
94. GOMEZ, D. M., *Rev. Sci.*, No. 3272 (May 1, 1947)
95. GOMEZ, D. M., *Federation Proc.*, **7**, 41–42 (1948)

96. Elkinton, J. R., Winkler, A. W., and Danowski, T. S., *J. Clin. Invest.*, **27**, 74–81 (1948)
97. Ekehorn, G., *Acta Med. Scand.*, **124**, 379–403 (1946)
98. Ekehorn, G., *Acta Med. Scand.*, **124**, 494–510 (1946)
99. Ekehorn, G., *Acta Med. Scand.*, **125**, 148–70 (1946)
100. Ekehorn, G., *Acta Med. Scand.*, **126**, 117–39 (1946)
101. Ekehorn, G., *Acta Med. Scand.*, **126**, 370–83 (1946)
102. Ekehorn, G., *Acta Med. Scand.*, **126**, Suppl. 185 (1946)
103. Barclay, J. A., and Kenney, R. A., *Acta Med. Scand.*, **125**, 386–93 (1946)
104. Berliner, R. W., and Kennedy, T. J., Jr., *Proc. Soc. Exptl. Biol. Med.*, **67**, 542–45 (1948)
105. Mudge, G. H., Foulks, J., and Gilman, A., *Proc. Soc. Exptl. Biol. Med.*, **67**, 545–47 (1948)
106. Pitts, R. F., Lotspeich, W. D., Schiess, W. A., and Ayer, J. L., *J. Clin. Invest.*, **27**, 48–56 (1948)
107. Schiess, W. A., Ayer, J. L., Lotspeich, W. D., and Pitts, R. F., *J. Clin. Invest.*, **27**, 57–64 (1948)
108. Pitts, R. F., Ayer, J. L., and Schiess, W. A., *Federation Proc.*, **7**, 94 (1948)
109. Sartorius, O. W., Roemmelt, J. C., and Pitts, R. F., *Federation Proc.*, **7**, 108 (1948)
110. Jahan, I., and Pitts, R. F., *Federation Proc.*, **7**, 61 (1948)
111. Wolf, A. V., *Am. J. Physiol.*, **148**, 54–68 (1947)
112. Phillips, R. A. (Unpublished data)
113. Winkler, A. W. (Unpublished data)
114. Van Slyke, D. D., *J. Clin. Invest.*, **26**, 1159–67 (1947)
115. Dole, V. P., *Am. J. Physiol.*, **139**, 504 (1943)
116. Bing, J., *Acta Med. Scand.*, **126**, 199 (1946)
117. Williams, E. M. V., *J. Physiol. (London)*, **105**, 223 (1946)
118. Wright, L. D., Russo, H. F., Skeggs, H. R., Patch, E. A., and Beyer, K. H., *Am. J. Physiol.*, **149**, 130–34 (1947)
119. Ferguson, F. P., Eaton, A. G., and Ashman, J. S., *Proc. Soc. Exptl. Biol. Med.*, **66**, 582–85 (1947)
120. Eiler, J. J., Althausen, T. L., and Stockholm, M., *Proc. Soc. Exptl. Biol. Med.*, **56**, 67–70 (1944)
121. Ahlborg, N. G., *Acta Physiol. Scand.*, **12**, 5–78 (1946)
122. Friedman, M., *J. Clin. Invest.*, **26**, 815–19 (1947)
123. Pitts, R. F., *Am. J. Physiol.*, **140**, 156 (1943)
124. Roemmelt, J. C., Sartorius, O. W., and Pitts, R. F., *Federation Proc.*, **7**, 104 (1948)
125. Cizek, L. J., and Holmes, J. H., *Federation Proc.*, **7**, 21 (1948)
126. Wesson, L. G., Anslow, W. P., Jr., and Smith, H. W., *Federation Proc.*, **7**, 132 (1948)
127. Mokotoff, R., Ross, G., and Leiter, L., *J. Clin. Invest.*, **27**, 1–9 (1948)
128. Lotspeich, W. D., Swan, R. C., and Pitts, R. F., *Am. J. Physiol.*, **148**, 445–48 (1947)
129. Redish, J., West, J. R., Whitehead, B. W., and Chasis, H., *J. Clin. Invest.*, **26**, 1043–45 (1947)

130. Shapiro, B., *Biochem. J.*, **41**, 151–54 (1947)
131. Morehead, R. P., and Little, J. M., *Am. J. Path.*, **21**, 339–55 (1945)
132. Bloom, F., *Arch. Path.*, **28**, 236–45 (1939)
133. Glynn, J. H., *Am. J. Path.*, **13**, 593–604 (1937)
134. Simonds, J. P., Linn, H. J., and Lange, J., *Arch. Path.*, **41**, 185–202 (1946)
135. Freeman, S., Rhoads, P. S., and Yeager, L. B., *J. Am. Med. Assoc.*, **130**, 197–202 (1946)
136. Danowski, T. S., Winkler, A. W., and Peters, J. P., *Ann. Internal. Med.*, **23**, 22 (1945)
137. Lowenhaupt, E., and Greenberg, D. M., *Arch. Path.*, **42**, 49–55 (1946)
138. Baxter, J. H., and Ashworth, C. T., *Arch. Path.*, **41**, 476–88 (1946)
139. Fishman, W. H., and Govier, W. H., *Science*, **101**, 277–79 (1945)
140. Freeman, S. (Personal communication, 1947)
141. Freeman, S., Li, T. W., and Wong, C. C., *Federation Proc.*, **5**(2), 30 (1946)
142. Dock, W., *Ann. Rev. Physiol.*, **9**, 244 (1947)
143. Cuthbertson, E. M., and Greenberg, D. M., *J. Biol. Chem.*, **160**, 83–94 (1945)
144. Addis, T., MacKay, E. M., and MacKay, L. L., *J. Biol. Chem.*, **71**, 157 (1926–27)
145. Hay, E. C., and Seguin, P., *Am. J. Physiol.*, **147**, 299–305 (1946)
146. Menten, M. L., and Janouch, M., *Proc. Soc. Exptl. Biol. Med.*, **63**, 33–37 (1946)
147. Morehead, R. P., Fishman, W. H., Artom, C., *Am. J. Path.*, **22**, 385–93 (1946)
148. Cavelti, P. A., and Cavelti, E. S., *Arch. Path.*, **39**, 148–52 (1945)
149. Cavelti, P. A., and Cavelti, E. S., *Arch. Path.*, **40**, 158–62 (1945)
150. Cavelti, P. A., and Cavelti, E. S., *Arch. Path.*, **40**, 163–72 (1945)
151. Gukelberger, M., and Monteil, R., *Schweiz. med. Wochschr.*, **74**, 32 (1944)
152. Gukelberger, M., and Tschumi, H., *Schweiz. med. Wochschr.*, **74**, 33 (1944)
153. Gukelberger, M., *Helv. Med. Acta*, **13**, 433–36 (1946)
154. Pressman, D., and Keighley, G., *J. Immunol.*, **59**, 141–46 (1948)
155. Marvel, C. S., Elliott, J. R., Boettner, F. E., and Yuska, H., *J. Am. Chem. Soc.*, **68**, 1681–86 (1946)
156. Perlstein, D., Liebmann, A. J., Wright, H. E., and Murtaugh, J. J., *Yale J. Biol. Med.*, **18**, 11–13 (1945)
157. Abbott, W. E., and Shea, P., *Am. J. Med. Sci.*, **211**, 312–19 (1946)
158. Fine, J. J., Frank, H. A., and Seligman, A. M., *Ann. Surg.*, **124**, 857 (1946)
159. Reid, R., Penfold, J. B., and Jones, R. N., *Lancet*, 749 (Nov. 23, 1946)
160. Goodpaster, W. E., Levenson, S. M., Tagnon, H. J., Lund, C. C., and Taylor, F. H. L., *Surg. Gynecol. Obstet.*, **82**, 652–70 (1946)
161. Scarff, R. W., and Keele, C. A., *Brit. J. Exptl. Path.*, **24**, 147–49 (1945)
162. Badenoch, W. W., and Darmady, E. M., *J. Path. Bact.*, **59**, 79 (1947)
163. Hamilton, P. B., Phillips, R. A., and Hiller, A., *Am. J. Physiol.*, **152**, 517–22 (1948)
164. Koletsky, S., and Gustafson, G. E., *J. Clin. Invest.*, **26**, 1072–78 (1947)
165. Reaves, J. U., *J. Urol.*, **57**, 65–72 (1947)
166. Corcoran, A. C., and Page, I. H., *J. Am. Med. Assoc.*, **134**, 436–41 (1947)

167. AMBERSON, W. R., FLEXNER, J., STEGGERDA, F. R., MULDER, A. G., TENDLE, M. J., PANKRATZ, D. S., AND LONG, E. P., *J. Cellular Comp. Physiol.*, **5**, 359 (1934–35)
168. DARDINSKI, V. J., *Am. J. Clin. Path.*, **15**, 286–88 (1945)
169. MAEGRAITH, B., *Trans. Royal Soc. Trop. Med. Hyg.*, **38**, 1–17 (1944)
170. PALMER, W. W., AND VAN SLYKE, D. D., *J. Biol. Chem.*, **32**, 499 (1917)
171. ROSS, G. R., *Research Mem. London School Trop. Med.*, No. 6 (1932)
172. BAKER, S. L., AND DODDS, E. C., *Brit. J. Exptl. Path.*, **6**, 247 (1925)
173. MAEGRAITH, B. G., HAVARD, R. E., AND PARSONS, D. S., *Lancet* (Sept. 8, 1945)
174. YUILE, C. L., *Physiol. Revs.*, **22**, 19–31 (1942)
175. MONKE, J. V., AND YUILE, C. L., *J. Exptl. Med.*, **72**, 149 (1940)
176. YUILE, C. L., STEINMAN, J. F., HAHN, P. F., AND CLARK, W. F., *J. Exptl. Med.*, **74**, 197–202 (1941)
177. YUILE, C. L., GOLD, M. A., AND HINDS, E. G., *J. Exptl. Med.*, **82**, 361–74 (1945)
178. BLACK, R. H., *Ann. Trop. Med. Parasitol.*, **42**, 90–94 (1948)
179. LALICH, J. J., *J. Exptl. Med.*, **86**, 153–57 (1947)
180. LALICH, J. J., *J. Exptl. Med.*, **87**, 157–62 (1948)
181. RATHER, L. J., *J. Exptl. Med.*, **87**, 163–73 (1948)
182. HARRISON, H. E., BUNTING, H., ORDWAY, N. K., AND ALBRINK, W. S., *J. Exptl. Med.*, **86**, 339–56 (1947)
183. FLINK, E. B., *J. Lab. Clin. Med.*, **32**, 223–61 (1947)
184. CORCORAN, A. C., AND PAGE, I. H., *Texas Repts. Biol. Med.*, **3**, 528–44 (1945)
185. AMBERSON, W. R., JACOBS, J. E., HISEY, A., AND MONKE, J. V., *Blood Substitutes and Blood Transfusion*, Chap. 19, 156 (Charles C Thomas, Springfield, Illinois, 1942)
186. AMBERSON, W. R., *Biol. Revs. Cambridge Phil. Soc.*, **12**, 48 (1937)
187. O'SHAUGHNESSY, L., MANSELL, H. E., AND SLOME, D., *Lancet*, 1068–69 (Nov. 18, 1939)
188. HUEPER, W. C., *J. Lab. Clin. Med.*, **29**, 628–32 (1944)
189. LAMSON, P. D., ROBBINS, B. H., AND GRIEG, M. E., *J. Pharmacol. Exptl. Therap.*, **83**, 225–34 (1945)
190. HAMILTON, P. B., FARR, L. E., HILLER, A., AND VAN SLYKE, D. D., *J. Exptl. Med.*, **86**, 455–63 (1947)
191. FARR, L. E., HILLER, A., AND VAN SLYKE, D. D., *J. Exptl. Med.*, **86**, 465–75 (1947)
192. PENNEL, R. B., AND SMITH, W. H., *Proc. Phil. Br. Am. Chem. Soc.* (Jan. 22, 1948)
193. HAMILTON, P. B., HILLER, A., AND VAN SLYKE, D. D., *J. Exptl. Med.*, **86**, 477–87 (1947)
194. PHILLIPS, R. A. (Unpublished data)

RADIATION[1]

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The Atomic Energy Commission, through its isotope distribution program, is making available to biological and medical investigators many powerful tools for biochemical and physiological research in quantities undreamed of a few years ago (1). Both stable and radioactive varieties of almost all elements in the periodic table can be obtained and are being used extensively in many research institutions in the United States and abroad (2, 3, 4). The scientists concerned with radioactive materials have a direct responsibility for developing the techniques of safe handling of potentially hazardous substances. This includes an understanding and evaluation of the subtle effects of ionizing radiation on plant and animal life which are basic to setting the safe levels of radiation exposure or the "tolerance dose" as defined by Cantril & Parker, applicable to external radiation (5). Morgan has outlined the procedures employed in determining the "tolerance concentrations" for ingested radioactive materials (6). The investigator needs to be aware of the possible health hazards connected with the use of radioactive substances (7, 8). Much more work is needed before the radiological toxicities of all the available isotopes are known, although sufficient information is at hand to make preliminary estimates of the dangers involved (9, 10, 11). All laboratories contemplating the use of radioactive isotopes would do well to adopt those procedures and rules of operation, where applicable, which contributed to the remarkable radiological safety record achieved by the Manhattan District and Atomic Energy Commission laboratories (12 to 16). The design of laboratories in which radioactive materials are to be used needs to be examined with great care, not only from the health safety point of view but also to minimize the possibilities of stray radioactive contamination influencing the results of a particular experiment (17, 18). A conservative attitude toward the exposure of personnel to ionizing radiation is thoroughly justified until better quantitative data is compiled concerning the

[1] This review covers the period from July, 1947 to July, 1948.

consequences of overexposure in man. One method of obtaining such data is outlined by Wilson & Greening (19).

Mechanism of action.—An excellent introduction to mechanisms of action of ionizing radiation on living cells and materials is contained in the symposium edited by Spear (20). From the results reported there and other information available in the literature, it is evident that many of the physiological effects of nuclear radiations observed in living systems are due to secondary chemical reactions resulting from the large amounts of energy absorbed. The target theory, while adequate to account for some of the genetic changes, needs to be supplemented when other aspects of the experiments on radiation are considered (21 to 25). Allen has demonstrated that all covalently-bonded substances suffer chemical change when exposed to ionizing radiation and that for each 100 electron volts of energy absorbed about four molecules in solution react (26). When two or more solutes are present, one is usually attacked preferentially, and very complex mixtures result from simple organic materials. There is sufficient production of free hydroxyl radicals and other components of energetically rich oxidation-reduction systems as Stein & Weiss (27) have shown to explain the inactivation of essential cellular enzyme systems so beautifully demonstrated by Barron *et al.* (28). That irradiation of water with x-rays can produce sufficient hydrogen peroxide to interfere with normal sperm function of *Arbacia punctulata* has been pointed out by Evans (29). Nucleic acid solutions in the hands of Taylor *et al.* (30) and synovial fluid studied by Ragan *et al.* (31) have a decreased viscosity after x-ray irradiation. Since the viscosity continues to decrease after the irradiation has ceased, there is strong indication that there are continuing chemical reactions which break up the larger protein molecules into smaller components.

Raper & Barnes attempted to settle the question of the nonspecificity of ionizing radiation by studying the possible additive effects of beta and gamma rays upon the production of lethality in mice. Their experiments indicate possibly different fundamental mechanisms of action but are not conclusive (32, 33). The injurious effects of neutron exposure are qualitatively similar to those seen with other forms of ionizing radiation. Zirkle points out that the amount of injury produced per unit of absorbed energy increases with the specific ionization of the radiation and that fast neutrons

may be up to twenty times as effective as x- or gamma radiation on particular systems (34). The calculations of the ionization produced in tissues by neutrons is complex largely due to the fact that various nuclear processes contribute to the total effect (35, 36, 37). In particular, slow neutrons can react with hydrogen nuclei with subsequent emission of γ-rays (n-γ reaction) and with nitrogen nuclei with emission of protons (n-p reaction), giving additional sources of energetic ionization which can account for about half or more of the total biological effect (38, 39). Tobias *et al.* have investigated the effects of fission in animal tissue. They injected a small amount of colloidal uranium-235 oxide into rats and found that sublethal doses of slow neutron irradiation became lethal (40).

Further approaches to understanding of the mechanisms of radiation damage are being made by altering the temperature before or after irradiation. Patt *et al.* have found that frogs survive lethal doses of x-radiation for a longer time if chilled to 5°C. (41). Farberg has shown that in *Tradescantia* the chromosome aberrations are fewer at higher temperatures although lowering or raising temperature immediately preceding irradiation gives an increased number of chromosome breaks (42). Treatment of living systems with either ultraviolet or infra-red at levels of irradiation without demonstrable biologic effect alters the sensitivity of the material to ionizing irradiation. Swanson has found that infrared irradiation makes *Tradescantia* and *Aspergillus* more sensitive to x-irradiation as indicated by resultant chromosome abnormalities (43). In mice, evidence has been obtained by Ellinger that repair processes in the tissues are quite important in determining the extent of radiation damage. Simple fractionation of a lethal dose, that is, dividing the total exposure to x-rays over several days, decreases the mortality rate (44).

Comparative studies on the effectiveness of neutrons and gamma irradiations on somatic mutations and on somatic crossing-over in *Drosophila* carried out by Lefevre (45, 46) give a higher incidence of effects with neutrons than expected. Other comparative studies on the effectiveness of neutrons and x- or gamma radiations indicate that the effectiveness of the various forms of radiation in producing a given change in a biological system is dependent upon the system studied and the method used to assay the results. Sacher & Pearlman found fast neutrons to be six times as effective as 200 Kv. x-rays in producing heterophil and lymphocyte

changes in rabbits' blood (47). Gray & Read observed that neutron irradiation was twenty-four times as effective in destroying a carcinoma *in vivo* as x-irradiation, but was only nine times as effective *in vitro* (48). All comparisons were made at the same calculated ionization per cc. of tissue. The wide discrepancy in biological effectiveness found is indicative of the unsettled nature of the problems involved. It is evident that any theory of the biological action of ionizing radiation must take full cognizance of the biochemistry and physiology of the living system under examination. From the biological point of view the observations of Giles on the radiation induced reversions of *Neurospora crassa* (49) or the experiments in the production of the relatively radiation resistant strains of *Escherichia coli* by Witkin (50) serve to accentuate our lack of knowledge and understanding of the important field of radiobiology. Spencer & Stern have checked the reliability of the linear dose mutation frequency relation over the range 25 to 4,000 r (51). They find with x-rays that the mutation rate is twice the spontaneous rate at 50 r in *Drosophila*.

Whole body radiation.—Henshaw & Snider believe that the most sensitive tissues in the animal body to penetrating radiations are those that are continually proliferating such as the lymph nodes, the germinal epithelium of the testis, or the hemopoietic tissues (52). There is a great deal of species variation, for Lorenz *et al.* find the hemopoietic system of rabbits to be relatively resistant to low level chronic exposures to gamma rays whereas that of the guinea pig is radiosensitive (53). The experiments of Welander *et al.* on the effects of x-rays on the larvae of the Chinook salmon (54) and those of Foster on young Rainbow trout (55) bear out the conclusion that the gonads in these species are very sensitive to ionizing radiation. Lorenz & Heston have shown for gamma irradiation that a total dose of 465 r at the rate of 4.4 r per day will permanently sterilize female mice. They found no damage to mice chromosomes when the levels of exposure were below 1.1 r per day. This was verified by the fact that mice had a normal life span and normal litter size in five subsequent generations when reared in a gamma irradiation field of such an intensity that exposures of 1.1 r per day and below were produced (56). Further studies are needed to firmly establish the dose level which does appreciably affect the spontaneous mutation rate in higher mammals (57), even though an exposure of 0.1 r a day appears to be

reasonable tolerance at which genetic and other effects of radiation appear to be minimal (58 to 62).

Exposure of laboratory animals to massive doses of irradiation produces a sequence of pathological changes which is proportional to both the dose rate and the total accumulated dose as indicated by the work of Prosser *et al.* (63). The relation between large single doses of ionizing radiation in the rat, dog, and monkey and mortality has been found by Boche & Bishop to be of a familiar sigmoid type (64). There is considerable variation among the species studied with respect to the median lethal dose, and major differences exist in the manner in which various species respond to irradiation damage. The sequence of events following lethal exposure of rabbits to x-rays has been outlined by Painter *et al.* (65) and Hagen *et al.* (66). A rapid drop in blood pressure, maximal at one to two hours after exposure, is often seen in animals that survive the initial shock; the blood pressure may fall again some eight to twelve days later when the animal dies. Deaths tend to group around definite periods after exposure, demonstrating several possible mechanisms through which the lethal action of penetrating radiation is expressed. Water balance is disturbed; diarrhea, listlessness, loss in weight, and hemorrhages occur, with a similar picture for both internal and external irradiation (67, 68). It is doubtful whether any of the body tissues escape either primary or secondary damage after massive irradiation. The full complexities of the clinical picture can only be appreciated by a study of the original reports. In contrast to the lethal effect of a few hundred r on mammals is the average lethal dose of 600,000 r of x-rays for lower organisms (range 20,000 to 1,250,000 r) such as bacteria, yeasts, micro-plankton, and other lower organisms as was found by Bonham *et al.* (69). The wide range of sensitivity of different living cells and different species is a challenging problem to the radiobiologist.

A few human subjects have been exposed to massive whole body irradiation. Craver reports on patients who had advanced metastatic malignant neoplasms and were given x-irradiation at the rate of 15 r per day up to 300 r without deterioration in blood count or the production of other deleterious effects directly ascribable to the irradiation (70). The application of these results to healthy humans must be viewed with great caution since the animal data indicate grave effects at much lower doses. The human

survivors of the atomic bomb explosions are still and will continue to be intensively studied and should furnish much needed information of the effects of a single massive exposure of mixed radiation to human beings (71, 72, 73). It is encouraging that disturbances of the hemopoietic tissue observed in these individuals in 1945 have returned approximately to normal by 1947. Warren points out in his report that there can be no satisfactory data on gene changes in these individuals for some twenty-five years (74). The immediate pathological picture observed in the fatalities due to irradiation following the Nagasaki and Hiroshima disasters as outlined by DeCoursey (75) is very similar to that observed in experimental animals. The outstanding symptoms before death include nausea and vomiting which occurred immediately after the bombing, followed by fever, leukopenia, and diarrhea. Late effects include epilation and purpura. The gastrointestinal tract was one of the first sites to present evidence of gross lesions. The problems the physicians have to face in atomic warfare have been outlined by Warren and thought is being given to protective measures for populated areas which might be attacked in the future (76).

Blood and hemopoiesis.—The blood forming organs in both animals and man are particularly sensitive to ionizing radiation. Eschenbrenner has studied the effects of low level exposure in guinea pigs (77). He finds that the majority of guinea pigs exposed daily to a gamma radiation at levels of 2.2 r and 4.4 r per day eventually die of anemia and thrombocytopenia. Dogs, in the hands of Prosser & Moore, exposed to x-rays at the dose rate of 12.5 r and 25 r daily developed a severe leukopenia and an aplastic bone marrow (78). Bloom & Jacobson have found no evidence for a stimulation of hematopoiesis with either internal or external radiation, though secondary or compensating increases may be seen in some of the cellular constituents of blood (79). The major sites of injury following exposure to both x-rays and protons appear to be the bone marrow, lymph nodes, and spleen in the experiments carried out by Suter (80). Splenectomized white rats exposed to massive doses of x-rays did not show a significant change in the leukocyte count though the lymphopenia was as severe as that produced in normal rats (81).

Jacobson has summarized the hematological effects which might be expected to occur following chronic exposure of human beings to low level irradiation and the types of studies made on the

plutonium projects which gave the basis for the protective measures employed (82). In persons chronically exposed to low level ionizing irradiation, a significant decrease in total leucocyte counts has been demonstrated by Dickie & Hempelmann (83). There was also found an increase in the number of refractive neutral red bodies in the cytoplasm of the circulating lymphocytes. Schwartz *et al.* believe that in both acute and chronic radiation exposure, destruction of circulating red cells is due in part to some hemolytic reaction, since the circulating red cells seem to disappear much faster than can be accounted for by inhibition of erythropoiesis (84). Brown has observed changes in the platelet count (85) and Setala finds fluctuations are produced in chylomicron count following irradiation (86). The platelet count may prove to be a useful indicator of incipient bone marrow damage. Sacher & Pearlman have examined the dose response and the time response curves of of the circulating heterophils and lymphocytes in rabbits after single exposures to x-rays (87). They find a simple functional relation between dose and amount of depression produced. The time response curves indicate at least two modes of injury. Lawrence *et al.*, in a study of the leucocyte and lymphocyte counts in cats, paired in cross-circulation experiments, find no evidence for indirect effect on hemopoiesis peculiar to radiation (88).

The possibility that the blood forming organs might be more sensitive to irradiation during a phase of increased proliferation has been tested by Jacobson *et al.* in animals with a regenerative anemia (89, 90) and by Jacobson in rats with a cobalt induced polycythemia (91) and has been found not to be true. These findings would seem to indicate that the general rule "increased proliferation means increased sensitivity to irradiation" has many exceptions.

The use of various agents to alleviate some of the postirradiation sequelae has been but partially successful. Hemorrhagic diathesis is less pronounced in rutin-fed dogs according to Rekers & Field (92, 93) and recovery from local irradiation damage was more prompt in rutin-fed rats than in untreated control rats in the experiments of Griffith *et al.* (94). Folic acid appears to prolong the survival time of heavily irradiated mice although it does materially affect the postirradiation pathological changes in the formed elements of the blood (95, 96, 97). Painter & Moore point out that laboratory animals are more sensitive to histamine and adeno-

sine for several hours after x-irradiation (98) suggesting perhaps that antihistamine drugs might partially prevent the shock-like state that often ensues.

Adams & Lawrence found that irradiation of the abdominal viscera of cats at the rate of 100 r per day produces a definite fall in the leukocyte and lymphocyte count (99). In whole body radiation, as Valentine *et al.* show, the total number of lymphocytes in the thoracic duct lymph falls rapidly after 1,500 r exposure without a marked reduction in the volume of lymph flow (100). The visceral lymphoid tissues appear to contain about a four hours' supply of lymphocytes or can supply about 50 to 60 per cent of the total number of lymphocytes in the blood before exhaustion takes place. Despite the marked fall in lymphocytes produced by x-irradiation, Craddock *et al.* have found no corresponding change in circulating antibodies in the thoracic lymph of the cat (101). The increase that occurred in the blood of some of the animals must have had some other source than lymphoid tissue drained by the thoracic duct. Craddock & Lawrence also found that exposure of rabbits to 250 r whole body x-ray irradiation, eight hours prior to immunization, causes a diminished antibody response despite the fact that after antibody formation has begun, x-radiation is without effect (102). Muntz *et al.* found no immediate changes in the blood proteins of dogs following massive irradiation (103). Seven days after exposure the albumin fraction began to fall and other late changes observed include striking increases in the alpha globulin and smaller increases in the beta globulin-fibrinogen fraction following the onset of fever. Daily exposure of dogs to low level x-irradiation up to 10 r per day was found by Fink to be without effect on the serum protein, serum chloride, serum cholesterol, nonprotein nitrogen, serum acid, and alkaline phosphatase levels of the blood of dogs (104). External beta irradiation in the dose range of 1,500 to 59,000 rep[2] was without direct effect on the cellular constituents of blood in the experiments of Raper & Barnes (105). Anderson points out that beta ray burns cannot be compared with thermal burns since the hematocrit is unaffected after 7,000 rep of beta ray exposure (106). The results suggest that plasma is lost to a beta ray damaged area at a very slow rate.

[2] " . . . roentgen equivalent physical (rep) is that quantity of ionizing radiation which is capable of producing 1.615×10^{12} ion pairs per gram of tissue" [see (155), footnote p. 482].

Skin.—As might be expected, the greatest effect of external beta irradiation is on the skin because of the weak penetrating power of beta rays. Inflammation erythemia, epilation, and desquamation develop with a severity more or less proportinal to the dose in all laboratory animals (107, 108). Bishop has found that about three times the exposure of beta rays in rep units is required to produce an effect equivalent to that seen with 30 Kv. x-rays (109). Knowlton *et al.* observed that the mitotic activity of the skin is reduced to very low levels immediately after exposure to x-rays and returns to normal and supernormal levels more or less rapidly depending on the magnitude of the dose (110). Wirth & Raper distinguish between two responses of the human skin to beta irradiation: a tanning reaction which occurs at 200 rep and an erythemia reaction which begins at about 700 rep exposure (111).

Doses of above 800 r of x-ray are required in monkeys and above 600 r in humans according to the observations of Harvey (112) and Nickson (113) to produce loss of finger ridge detail. Despite the large dosage required, over half the radiologists examined by Harvey (114) and by Nickson (115) had ridge abnormalties in the finger print area. Changes were also found by Nickson in the morphology of capillaries in the nail fold area in individuals with moderate exposure to radioactive materials (116). Further studies similar to these are necessary to establish whether a practical use could be made of these effects in the matter of exposure control. The delayed effects of overexposure to beta irradiation include alopecia, atrophy, keratosis, and tumor production in laboratory animals (117, 118, 119). Tumors, epidermal in origin, may appear in four to five months after a single exposure to 4,000 rep of beta rays. Massive injections of glucose reduce somewhat the sensitivity of the skin to x-rays (120).

Other tissues.—Patt *et al.* have found that whole body x-irradiation at levels at 650 r and above stimulates considerable adrenal gland activity as indicated by changes in the adrenal weight and adrenal cholesterol content (121). Craver has shown that shielding the adrenal gland during whole body radiation will partially protect irradiated rats (122), and Ellinger found that injection of desoxycorticosterone acetate not only protects mice from radiation-induced liver changes, but also brings about a drop in the mortality rate after x-ray exposure (123). That the transient fall in adrenal cholesterol observed shortly after whole body ex-

posure to x-irradiation can be largely prevented by injection of adrenal cortical extract has been found by Swift *et al.* although survival is not enhanced by this treatment (124). From the experiments above it is evident that radiation stress affects the pituitary adrenal system in a manner similar to other forms of stress. Whether effective therapeutic measures based upon this knowledge can be found awaits further experimentation.

Brues *et al.* have observed that the weights of the visceral organs are more constant than is the body weight as a whole, and that the weight changes with chronic x-irradiation at a level of 14 r per day are similar to those seen in inanition (125). The radiosensitive tissues, of course, are exceptions. Local irradiation of the brain of dogs produces remarkable increases of the globulin fraction of the blood and a threefold increase in the carbohydrate utilization of the brain according to the observations of Blokhin (126). Isolated strips of the small intestine of the cat retained their motility with doses of soft x-rays up to 10,000 r in experiments carried out by Craver (127). This experiment is difficult to reconcile with the observations of Barron *et al.*, who find evidence of serious interference with carbohydrate and phosphorus metabolism in the small intestine of rats who had received whole body x-radiation. Four hours after exposure they found an abrupt fall in respiration, a diminished absorption of glucose, and a diminished phosphorylation of fructose (128).

Internal radiation.—Radioisotopes can be used as sources for internal radiation, and by virtue of being incorporated into sensitive cellular constituents may prove to be more effective in producing radiation damage than external sources of radiation, as the experiments of Powers on *Paramecium aurelia* seem to indicate (129). He found that radioactive phosphorus which enters the cell was at least four times as effective in producing death after autogamy as a radioactive strontium-yttrium mixture which does not. Both sources of radiation were employed at the same level of ionization produced in air. Germinating seeds treated with or grown in soil containing radioactive phosphorus not only give plant cells with large numbers of chromosome abnormalities, but also give a greatly increased rate of mutation (130,131). The lethal effects of radioactive phosphorus present in the media in which *Escherichia coli* are grown have been studied by Schmidt (132). He points out that it would be extremely difficult to use radioactive materials

for food sterilization, since very high levels of activity are unsuccessful in destroying the viability of all the cells.

Many radioactive isotopes have high radiological toxicities because they tend to deposit in certain tissues in high concentrations. Anthony & Lathrop have found that cerium^{144} is retained in the liver for some period of time and can produce marked signs of injury (133). Some gets to the bone and in a few animals osteogenic sarcomas were produced. Strontium^{89} is eliminated quite rapidly after intravenous injection and the small amounts that remain are present in the skeleton at a concentration more than a hundredfold higher than that in the soft tissues (134, 135). The LD_{60} for rats of strontium^{89} was found to be 5μc. per gm. by Lathrop & Snyder (136). Yttrium^{91} was found to be retained in large part by the liver of male rats in the experiments performed by Anthony (137). Following the injection of yttrium^{91} at a dose of 20 μc. per gm., Jacobson & Simmons observed a marked initial elevation of the erythrocytes and hemoglobin of rats, followed by an erratic anemia due to hemorrhage (138). In this experiment a 75 per cent reduction of lymphocytes was produced within three days and the count did not return to normal until forty-two days had passed. Radium and plutonium produce an overgrowth of bone of an atypical fibrous structure. Three months after injection of 0.3 μc. per gm. of radium and seven months after 0.03 μc. per gm. of plutonium, atypical proliferated changes in the bone occurred which, according to Bloom & Bloom, may represent early sarcoma or a predisposing state (139). Radioactive barium-lanthanum mixtures injected intraperitoneally into mice was found by Finkle *et al.* to give an LD_{60} dose at the 5 μc. per gm. level (140). The animals showed outward signs of injury before death. These consisted of loss of hair, development of watery eyes, and encrusted lids. Though lethargic, the animals were quite nervous and irritable when disturbed. Snyder *et al.* found a definite retardation in growth to occur at about half of the LD_{50} dose of the radioactive barium-lanthanum mixture (141). The LD_{50} dose of sodium^{24} was estimated by Finkle to be about 30 μc. per gm. for rats and mice (142). Jacobson & Simmons showed that a moderate to severe leukopenia is produced by radioactive sodium at all levels above 12 μc. per gm. in male mice (143). Phosphorus^{32}, administered at the rate of 0.5 μc. per gm. per month and above, has been found by Lisco *et al.* to increase the incidence of lymphoma in CF-1 female mice (144). While the inci-

dence of mammary tumors was not increased in this strain, lung tumors did increase. It is possible to expose fetal mice to internal radiation since both strontium and plutonium pass the placental barrier with ease as pointed out by Finkel (145). The rats and mice exposed to radioactive strontium in utero and through milk supplied by the injected mothers show retardation in growth, malformation of the long bones, anemia, and osteogenic sarcoma. Gorbman has been able to obtain complete destruction of the thyroid glands in young mice by feeding radioiodine (146). A complete histological study of the rats' thyroid after administration of iodine^{131} to iodine-starved animals has been made by Findlay & Leblond (147). They found destructive lesions of the follicles in central position of the gland with some sparing of the peripheral follicles.

Radioactive iodine has been found useful in treatment of Graves' disease in man by Chapman (148). The criteria and use of iodine^{131} in several conditions, with manner of use, and protection measures needed has been outlined by Means (149). Evans *et al.* report that radioactive sodium relieves some of the symptoms of chronic myelogenous and chronic lymphatic leukemia as well as those of polycythemia vera (150). The rate of response obtained during treatment appears to be intermediate between that obtained with exposures to x-ray or injection of radioactive phosphorus. A critical review by Doan *et al.* of the results obtained in one hundred clinical cases demonstrates radioactive phosphorus to be the treatment of choice in polycythemia vera, valuable as an adjunct to other treatments in the leukemias, and without effect on Hodgkin's disease (151). Craver compares the results obtained in the treatment of lymphomous leukemias and allied disorders by various methods and believes that considerable hope exists for a more specific attack on these disorders by modifications of radioactive isotope therapy (152). Radioactive colloidal gold may find a place in the treatment of diseases of the lymphoid system according to Sheppard *et al.* (153). Its short half life of 2.7 days and favorable radiation spectrum warrant greater application to experimental therapy than is being made at present. A review of the last fifty years' progress in radiotherapy by Finzi emphasizes the potentialities of the isotopes now available not only for therapeutic purposes, but also for physiological and pharmacological research (154). From the work done up to the present time with radioac-

tive isotopes in the medical field, it is evident that greatest advances will come, not from the use of isotopes as sources of internal radiation, but from the employment of tracer techniques to gain a further understanding of the physiological disturbances and pathological processes characteristic of the diseased states.

No attempt has been made to cover the whole field of radiobiology in this review. The genetic effects of radiation in particular must be looked for elsewhere. Last year's review by Dobson & Lawrence (155) considers in detail the effects of specific radiations. An international bibliography on the scientific aspects of atomic energy is now under preparation. The preliminary edition of part III, "The Biological and Medical Effects of High Energy Radiation," and of part IV, "Isotopes in Biology and Medicine," will be available soon and should be of great benefit to the biological and medical workers in this field (156).

LITERATURE CITED

1. *U. S. Atomic Energy Commission, Fourth Semi-annual Report*, 192 pp. (U. S. Government Printing Office, 1948)
2. KAMEN, M. D., *Radioactive Tracers in Biology*, 281 pp. (Academic Press, Inc., New York, 1948)
3. SACKS, J., *Chem. Revs.*, **42**, 411–56 (1948)
4. LAWRENCE, J. H., AND HAMILTON, J. G., *Advances in Biological and Medical Physics*, 484 pp. (Academic Press, Inc., 1948)
5. CANTRIL, S. T., AND PARKER, H. M., *Atomic Energy Commission Declassified Document No. MDDC-1100* (1945)
6. MORGAN, K. Z., *J. Phys. & Colloid Chem.*, **51**, 984–1003 (1947)
7. MORGAN, K. Z., *U. S. Naval Med. Bull.*, Suppl. 142–60 (March-April, 1948)
8. BROWN, D. F., *Proc. Confr. Nuclear Chem. Inst. Canada*, 205–11 (1947)
9. COHN, W. E., *Nucleonics*, **3**, 21–26 (1948)
10. LISCO, H., *U. S. Naval Med. Bull.*, Suppl. 161–63 (March-April, 1948)
11. MORGAN, K. Z., *Atomic Energy Commission Declassified Document No. MDDC-240* (1947)
12. MORGAN, K. Z., *Chem. Eng. News*, **25**, 3794–98 (1947)
13. CURTISS, L. F., *Am. Ind. Hyg. Assoc. Quart.*, **8**, 14–18 (1948)
14. U. S. Atomic Energy Commission, Clinton Laboratories, *Rules and Procedures Concerning Radioactive Substances and Associated Hazards* (PBL-92185), 30 pp. (February, 1947)
15. WIRTH, J. E., *Atomic Energy Commission Declassified Document No. MDDC-247* (1947)
16. SULLIVAN, W. H., *Chem. Eng. News*, **25**, 1862–65 (1947)
17. TOMPKINS, P. C., *U. S. Naval Med. Bull.*, Suppl. 164–75 (March-April, 1948)
18. TOMPKINS, P. C., BROIDO, A., AND TERESI, J. D., *Atomic Energy Commission Declassified Document No. MDDC-377* (1947)

19. WILSON, C. W., AND GREENING, J. R., *Brit. J. Radiology*, **21**, 211–20 (1948)
20. SPEAR, F. G., *Brit. J. Radiology*, **20**, Suppl. 1, 146 pp. (1947)
21. WEISS, J., *Trans. Faraday Soc.*, **43**, 314–24 (1947)
22. VAN DER WERFF, J. T., *Acta Radiol.*, **28**, 169–84 (1947)
23. ALLSOPP, C. B., *Brit. J. Radiology*, **21**, 72–74 (1948)
24. NEU, L., AND NEU, V., *Med. Woman's J.*, **54**, 17–23 (1947)
25. MINDER, W., *Radiolog. Clin.*, **16**, 73–81 (1947)
26. ALLEN, A. O., *Atomic Energy Commission Declassified Document No. MDDC-962* (1947)
27. STEIN, G., AND WEISS, J., *Nature*, **161**, 650 (1948)
28. BARRON, E. S. G., DICKMAN, S. R., SINGER, T. P., AND MUNTZ, J. A., *Atomic Energy Commission Declassified Document No. MDDC-1131* (1946)
29. EVANS, T. C., *Biol. Bull.*, **92**(2), 99–109 (1947)
30. TAYLOR, B., GREENSTEIN, J. P., AND HOLLAENDER, A., *Arch. Biochem.*, **16**, 19 (1948)
31. RAGAN, C., DONLAN, C. P., COSS, J. A., JR., AND GRUBIN, A. F., *Proc. Soc. Exptl. Biol. Med.*, **66**, 170–72 (1947)
32. RAPER, J. R., AND BARNES, K. K., *Atomic Energy Commission Declassified Document No. MDDC-498* (1947)
33. RAPER, J. R., AND BARNES, K. K., *Atomic Energy Commission Declassified Document No. MDDC-1681* (1947)
34. ZIRKLE, R. E., *Atomic Energy Commission Declassified Document No. MDDC-444* (1947)
35. MITCHELL, J. S., *Brit. J. Radiology*, **20**, 177–80 (1947)
36. STONE, R. S., *Am. J. Roentgenol. Radium Therapy*, **59**, 771–85 (1948)
37. WILSON, H. A., *Atomic Energy Commission Declassified Document No. MDDC-1025* (1943)
38. MITCHELL, J. S., *Brit. J. Radiology*, **20**, 79–82 (1947)
39. ZIRKLE, R. E., *Radiology*, **49**, 271–73 (1947)
40. TOBIAS, C. A., WEYMOUTH, P. P., WASSERMAN, L. R., AND STAPLETON, G. E., *Science*, **107**, 115 (1948)
41. PATT, H. M., SWIFT, M. N., AND TYREE, E. B., *Federation Proc.*, **7**, 90–91 (1948)
42. FABERG, A. C., *Genetics*, **33**, 104 (1948)
43. SWANSON, C. P., *Science*, **107**, 458 (1948)
44. ELLINGER, F., *Radiology*, **49**, 238–41 (1947)
45. LEFEVRE, G., JR., *Genetics*, **33**, 112 (1948)
46. LEFEVRE, G., JR., *Genetics*, **33**, 113 (1948)
47. SACHER, G. A., AND PEARLMAN, N., *Atomic Energy Commission Declassified Document No. MDDC-1337* (1946)
48. GRAY, L. H., AND READ, J., *Brit. J. Radiology*, **21**, 5–10 (1948)
49. GILES, N. H., JR., *Atomic Energy Commission Declassified Document No. AECD-2068* (1947)
50. WITKIN, E. M., *Genetics*, **32**, 221–48 (1947)
51. SPENCER, W. P., AND STERN, C., *Genetics*, **33**, 43–73 (1948)
52. HENSHAW, P. S., AND SNIDER, R. S., *Atomic Energy Commission Declassified Document No. MDDC-569* (1947)
53. LORENZ, E., HESTON, W. E., JACOBSON, L. O., ESCHENBRENNER, A. B.,

SHIMKIN, M., DERINGER, M. K., AND DONIGER, J., *Atomic Energy Commission Declassified Document No. MDDC-655* (1947)
54. WELANDER, A. D., DONALDSON, L. R., FOSTER, R. F., BONHAM, K., AND SEYMOUR, A. H., *Growth*, **12**, 203–42 (1948)
55. FOSTER, R. F., *Atomic Energy Commission Declassified Document No. AECD-2079* (1948)
56. LORENZ, E., AND HESTON, W. E., *Atomic Energy Commission Declassified Document No. MDDC-653* (1947)
57. ELLIS, F., *Brit. J. Radiology*, **21**, 1–4 (1948)
58. LORENZ, E., *Atomic Energy Commission Declassified Document No. MDDC-656* (1946)
59. LORENZ, E., ESCHENBRENNER, A. B., DERINGER, M. K., AND HESTON, W. E., *Cancer Research*, **6**, 485 (1948)
60. LORENZ, E., *Atomic Energy Commission Declassified Document No. MDDC-654* (1947)
61. EVANS, T. C., *Radiology*, **50**, 811–34 (1948)
62. HENSHAW, P. S., SNIDER, R. S., RILEY, E. F., STAPLETON, G. E., AND ZIRKLE, R. E., *Atomic Energy Commission Declassified Document No. MDDC-754* (1946)
63. PROSSER, C. L., PAINTER, E. E., LISCO, H., BRUES, A. M., JACOBSON, L. O., AND SWIFT, M. N., *Radiology*, **49**, 299–313 (1947)
64. BOCHE, R. D., AND BISHOP, F. W., *Atomic Energy Commission Declassified Document No. MDDC-250* (1947)
65. PAINTER, E. E., PROSSER, C. L., AND MOORE, M. C., *Atomic Energy Commission Declassified Document No. MDDC-761* (1947)
66. HAGEN, C. W., JR., JACOBSON, L. O., MURRAY, R., AND LEAR, P., *Atomic Energy Commission Declassified Document No. MDDC-999* (1944)
67. PROSSER, C. L., PAINTER, E. E., LISCO, H., BRUES, A. M., JACOBSON, L. O., AND SWIFT, M. N., *Atomic Energy Commission Declassified Document No. MDDC-1066* (1947)
68. HAGEN, C. W., JR., AND SIMMONS, E. L., *Atomic Energy Commission Declassified Document No. MDDC-1210* (1947)
69. BONHAM, K., SEYMOUR, A. H., DONALDSON, L. R., AND WELANDER, A. D., *Science*, **106**, 245–46 (1947)
70. CRAVER, L. F., *Atomic Energy Commission Declassified Document No. MDDC-993* (1945)
71. Genetic Effects of Atomic Bombing, *Lancet*, 292–93 (1948)
72. LEUCUTIA, T., *Am. J. Roentgenol. Radium Therapy*, **59**, 890–93 (1948)
73. HOWLAND, J. W., AND WARREN, S. L., *Cancer Research*, **6**, 449–53 (1946)
74. WARREN, S., *Military Surgeon*, **102**, 98 (1948)
75. DECOURSEY, E., *Military Surgeon*, **102**, 427–32 (1948)
76. WARREN, S. L., BRYAN, F. A., AND BUETTNER, R. J., *Ind. Med.*, **16**, 276–79 (1947)
77. ESCHENBRENNER, A. B., *Atomic Energy Commission Declassified Document No. MDDC-642* (1947)
78. PROSSER, C. L., AND MOORE, M. C., *Atomic Energy Commission Declassified Document No. MDDC-1271* (1946)
79. BLOOM, W., AND JACOBSON, L. O., *Blood*, **3**, 586–91 (1948)

80. Suter, G. M., *Atomic Energy Commission Declassified Document No. MDDC-824* (1947)
81. Stearner, S. P., Simmons, E. L., and Jacobson, L. O., *Atomic Energy Commission Declassified Document No. AECD-2022* (1947)
82. Jacobson, L. O., Marks, E. K., and Lorenz, E., *Atomic Energy Commission Declassified Document No. AECD-2085* (1947)
83. Dickie, A., and Hempelmann, L. H., *Atomic Energy Commission Declassified Document No. MDDC-1102* (1947)
84. Schwartz, S., Katz, E. J., Porter, L. M., Jacobson, L. O., and Watson, C. J., *Atomic Energy Commission Declassified Document No. MDDC-1342* (1946)
85. Brown, W. M. C., *Brit. J. Radiology*, **21**, 221–25 (1948)
86. Setala, K., *Radiology*, **50**, 803–9 (1948)
87. Sacher, G. A., and Pearlman, N., *Atomic Energy Commission Declassified Document No. MDDC-1274* (1946)
88. Lawrence, J. S., Valentine, W. N., and Dowdy, A. H., *Blood*, **3**, 593–609 (1948)
89. Jacobson, L. O., Marks, E. K., Gaston, E. O., Simmons, E. L., and Block, M. H., *Science*, **107**, 248–50 (1948)
90. Jacobson, L. O., Marks, E. K., Gaston, E. O., and Simmons, E. L., *Atomic Energy Commission Declassified Document No. MDDC-1004* (1947)
91. Jacobson, L. O., *Atomic Energy Commission Declassified Document No. AECD-2014* (1948)
92. Rekers, P. E., and Field, J. B., *Science*, **107**, 16–17 (1948)
93. Field, J. B., and Rekers, P. E., *Atomic Energy Commission Declassified Document No. MDDC-1672* (1948)
94. Griffith, J. Q., Jr., Anthony, E., Pendergrass, E. P., and Perryman, R., *Proc. Soc. Exptl. Biol. Med.*, **64**(3), 332–33 (1947)
95. Goldfeder, A., Cohen, L., Miller, C., and Singer, M., *Proc. Soc. Exptl. Biol. Med.*, **67**, 272–78 (1948)
96. Jacobson, L. O., Stearner, S. P., and Simmons, E. L., *Atomic Energy Commission Declassified Document No. AECD-2013* (1948)
97. Stearner, S. P., *Atomic Energy Commission Declassified Document No. AECD-2009-D* (1948)
98. Painter, E. E., and Moore, M. C., *Federation Proc.*, **7**, 90 (1948)
99. Adams, W. S., and Lawrence, J. S., *Atomic Energy Commission Declassified Document No. AECD-2006* (1948)
100. Valentine, W. N., Craddock, C. G., and Lawrence, J. S., *Atomic Energy Commission Declassified Document No. AECD-2023* (1948)
101. Craddock, C. G., Jr., Valentine, W. N., and Lawrence, J. S., *Atomic Energy Commission Declassified Document No. AECD-2095* (1948)
102. Craddock, C. G., and Lawrence, J. S., *Atomic Energy Commission Declassified Document No. MDDC-1698* (1948)
103. Muntz, J. A., Barron, E. S. G., and Prosser, C. L., *Atomic Energy Commission Declassified Document No. MDDC-371* (1947)
104. Fink, K., *Atomic Energy Commission Declassified Document No. MDDC-211* (1947)

105. RAPER, J. R., AND BARNES, K. K., *Atomic Energy Commission Declassified Document No. MDDC-579* (1947)
106. ANDERSON, E., *Atomic Energy Commission Declassified Document No. MDDC-534* (1947)
107. RAPER, J. R., *Radiology*, **49**, 314–24 (1947)
108. RAPER, J. R., AND BARNES, K. K., *Atomic Energy Commission Declassified Document No. MDDC-501* (1947)
109. BISHOP, F. W., *Atomic Energy Commission Declassified Document No. MDDC-203* (1946)
110. KNOWLTON, N. P., JR., HEMPELMANN, L. H., AND HOFFMAN, J. C., *Science*, **107**, 625 (1948)
111. WIRTH, J. E., AND RAPER, J. R., *Atomic Energy Commission Declassified Document No. MDDC-508* (1947)
112. HARVEY, R. A., *Atomic Energy Commission Declassified Document No. MDDC-215* (1947)
113. NICKSON, M., *Atomic Energy Commission Declassified Document No. MDDC-1269* (1947)
114. HARVEY, R. A., *Atomic Energy Commission Declassified Document No. MDDC-216* (1947)
115. NICKSON, M., *Atomic Energy Commission Declassified Document No. MDDC-1309* (1947)
116. NICKSON, M., *Atomic Energy Commission Declassified Document No. MDDC-1270* (1945)
117. RAPER, J. R., HENSHAW, P. S., AND SNIDER, R. S., *Atomic Energy Commission Declassified Document No. MDDC-578* (1947)
118. HENSHAW, P. S., AND SNIDER, R. S., *Atomic Energy Commission Declassified Document No. MDDC-570* (1947)
119. HENSHAW, P. S., AND SNIDER, R. S., *Atomic Energy Commission Declassified Document No. MDDC-1663* (1948)
120. BACLESSE, F., AND LOISELEUR, J., *Compt. rend. soc. biol.*, **141**, 743–45 (1947)
121. PATT, H. M., SWIFT, M. N., TYREE, E. B., AND JOHN, E. S., *Am. J. Physiol.*, **150**, 480–86 (1947)
122. CRAVER, B. N., *Federation Proc.*, **6**, 319 (1947)
123. ELLINGER, F., *Proc. Soc. Exptl. Biol. Med.*, **64**, 31–35 (1947)
124. SWIFT, M. N., PATT, H. M., AND TYREE, E. B., *Federation Proc.*, **7**, 121–22 (1948)
125. BRUES, A. M., SACHER, G. A., AND FRANCE, H. O., *Atomic Energy Commission Declassified Document No. MDDC-1197* (1946)
126. BLOKHIN, N. N., GRAEVSKAYA, B. M., AND KEILINA, R. YA., *Byull. Eksptl. Biol. Med.*, **23**, 338–42 (1947)
127. CRAVER, B. N., *Am. J. Roentgenol. Radium Therapy*, **58**, 357–58 (1947)
128. BARRON, E. S. G., WOLKOWITZ, W., AND MUNTZ, J. A., *Atomic Energy Commission Declassified Document No. MDDC-1241* (1947)
129. POWERS, E. L., JR., *Genetics*, **33**, 120 (1948)
130. ARNASON, T. J., CUMMING, E., AND SPINKS, J. W., *Science*, **107**, 198–99 (1948)
131. ARNASON, T. J., CUMMING, E., AND SPINKS, J. W., *Can. J. Research* [C]**26**, 109–14 (1948)

132. SCHMIDT, C. F., *J. Bact.*, **55**, 705–9 (1948)
133. ANTHONY, D. S., AND LATHROP, K. A., *Atomic Energy Commission Declassified Document No. MDDC-1326* (1947)
134. ANTHONY, D. S., LATHROP, K. A., AND FINKLE, R. D., *Atomic Energy Commission Declassified Document No. MDDC-1540* (1946)
135. ANTHONY, D. S., LATHROP, K. A., AND FINKLE, R. D., *Atomic Energy Commission Declassified Document No. MDDC-1363* (1947)
136. LATHROP, K. A., AND SNYDER, R. H., *Atomic Energy Commission Declassified Document No. MDDC-1364* (1946)
137. ANTHONY, D. S., *Atomic Energy Commission Declassified Document No. MDDC-1240* (1946)
138. JACOBSON, L. O., AND SIMMONS, E. L., *Atomic Energy Commission Declassified Document No. AECD-2037* (1946)
139. BLOOM, M. A., AND BLOOM, W., *Atomic Energy Commission Declassified Document No. AECD-2053* (1948)
140. FINKLE, R. D., SNYDER, R. H., AND KISIELESKI, W. E., *Atomic Energy Commission Declassified Document No. MDDC-1207* (1947)
141. SNYDER, R. H., SACHER, G. A., AND TERESI, J. D., *Atomic Energy Commission Declassified Document No. MDDC-1343* (1946)
142. FINKLE, R. D., *Atomic Energy Commisssion Declassified Document No. AECD-2011* (1946)
143. JACOBSON, L. O., AND SIMMONS, E. L., *Atomic Energy Commission Declassified Document No. AECD-2036* (1946)
144. LISCO, H., FINKEL, M. P., AND HIRSCH, G., *Atomic Energy Commission Declassified Document No. AECD-2009-E* (1948)
145. FINKEL, M. P., *Physiol. Zoöl.*, **20**, 405–21 (1947)
146. GORBMAN, A., *Proc. Soc. Exptl. Biol. Med.*, **66**, 212–13 (1947)
147. FINDLAY, D., AND LEBLOND, C. P., *Am. J. Roentgenol. Radium Therapy*, **59**, 387–95 (1948)
148. CHAPMAN, E. M., *Western J. Surg. Obstet., Gynecol.*, **56**, 1–64 (1948)
149. MEANS, J. H., *Bull. N. Y. Acad. Med.*, **24**, 273–86 (1948)
150. EVANS, T. C., LENZ, M., DONLAN, C. P., AND LEMAY, M. J., *Am. J. Roentgenol. Radium Therapy*, **59**, 469–81 (1948)
151. DOAN, C. A., WISEMAN, B. K., WRIGHT, C. S., GEGER, J. H., MEYERS, W., AND MEYERS, J. W., *J. Lab. Clin. Med.*, **32**, 943–69 (1947)
152. CRAVER, L. E., *Bull. N. Y. Acad. Med.*, **24**, 3–25 (1948)
153. SHEPPARD, C. W., GOODELL, J. P. B., AND HAHN, P. F., *J. Lab. Clin. Med.*, **32**, 1437–41 (1947)
154. FINZI, N. S., *Brit. J. Radiology*, **21**, 105–8 (1948)
155. DOBSON, R. L., AND LAWRENCE, J. W., *Ann. Rev. Physiol.*, **10**, 479–500 (1948)
156. *An International Bibliography on Atomic Energy. Scientific Aspects;* Part III. "The Biological and Medical Effects of High Energy Radiation"; Part IV. "Isotopes in Biology and Medicine" (United Nations Atomic Energy Commission, 1948)

PERMEABILITY

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This review attempts to present the main progress in the field of biological permeability made in the period of 1946–1947. The short space available, and the lack of many important periodicals or reprints, necessarily prevents a complete bibliography. As in previous reviews the reader is also referred to articles on absorption, secretion, etc., by special tissue systems (kidney, digestive system, liver, skin, muscle, placenta, capillaries, lymphatics, etc.) in this or previous volumes, as well as in the *Annual Review of Biochemistry*, for more complete reports on these topics. Works on plant permeability, although including many important bearings on animal problems, must unfortunately be omitted this year.

The reviewer is under the impression that output of papers on permeability has diminished in recent years. The reasons for this decline in interest are of course difficult to state, but one may venture the suggestion that permeability research in many sectors has entered into a cul-de-sac. The descriptive side of the subject is by now rather completely covered; an immense amount of analytical data has been collected, and a large number of theories, as to mechanisms, have been advanced. These facts do not signify, however, that our knowledge of permeability phenomena approach saturation. On the contrary, everybody familiar with this field knows that much remains to be clarified. It is the reviewer's opinion that the chief reason, which at present slows down the analysis of cell permeability is that too many biologists have been too eager to cut its "flowers" and too few have cared for its roots in the fundamental soil of the basic sciences of physics, physical chemistry, and chemistry. In order to justify to some extent this opinion, the present author, before starting to review recent papers, will make an attempt to diagnose some important deficiencies in current permeability research. The author also wants to make constructive suggestions pointing out directions in which an extended exploration is considered necessary. Such an effort of critical analysis, even if fragmentary and colored by the author's personal leanings perhaps may be more useful than a monotonous recitation of the products of the last years' work.

Some Critical Viewpoints on the Present Permeability Research

Ambiguity of the term "permeability."—The very term "permeability" is often used in an ambiguous way, especially in quantitative considerations. Many authors do not make a clear distinction between (*a*) the "permittivity" of a membrane[1] for the particular substance under investigation (i.e., the permeability in the proper, narrow sense) and (*b*) the driving forces, which create the very process of the substance transport (the permeation or penetration). These two factors will be discussed in greater detail on pp. 548–51. The rate of flow of substance across a membrane, i.e., the amount of substance crossing per time unit, is often described as "permeability" in a wider, kinetic sense. It is strange that it is not always apprehended that any such transport must arise from the simultaneous operation of both the factors (*a*) and (*b*); the presence of either of them does not alone lead to any penetration across the membrane.

False or apparent impermeability.—A questionable interpretation is frequently met with even in some recent careful studies: one investigator has found, for instance, that a certain substance X is present in a negligible concentration inside a given species of cell as compared with the concentration in its environment, leading to the conclusion that the cell is more or less impervious for X! This statement may be true, but not necessarily so. One alternative explanation is that X would easily pass the membrane were it not for the presence of an outwardly directed driving (resultant) force, which thus becomes responsible for the peculiar, unequal distribution of X. Unfortunately, it is not always easy to distinguish in a biological object between an alleged lack of permittivity on one hand and the nature, direction, and magnitude of the driving forces on the other. Indeed, of the many cases of substance depletion (or the reverse phenomenon called "accumulation") described in the experimental literature, hardly any include a satisfactory definition of the driving forces. In simple inanimate systems, however, both observation and theory confirm the possibility of an "apparent impermeability" owing to a peculiar super-

[1] For convenience the term "membrane" in this paper will include not only homogeneous membranes and phase boundaries in the usual physical sense, but also cell membranes, tissue boundaries, etc., of a composite structure.

position of driving forces. Straub *et al.* (1), for example, has recently described such experiments with inanimate membranes separating electrolyte solutions which agree fairly well with theoretical equations published long ago (2, 3).

Definitions of the permeability process (the transport).—It may now be instructive to summarize the intensity term of permeability in a compact form and somewhat briefly mention some consequences arising from it. In order to avoid the possible ambiguity of the word permeability one may exchange it for "flux" and define it as the amount of substance which per unit time penetrates per unit area (of an infinitesimal volume element) normal to the direction of transport. This definition is in conformity with Nernst & Planck's fundamental expressions for electrolyte transfer:

$$\text{Flux} = \text{mobility} \times \text{concentration} \times \text{total driving force.}$$

Here, of course, all factors refer to the given volume element and the force is defined per unit of activity or concentration. Only after the lapse of sufficient time will the flux be uniform in every cross section of the membrane, i.e., a steady state or equilibrium will be reached. It should be emphasized that the force can be composed not only of concentration (activity) gradients, but may also include superposed forces originating from electric potential, hydrostatic gradient, etc. (see pp. 548–51).

The emphasis here laid upon the word membrane should not be mistaken as an indication that the energy necessary for a continuous substance transport is always supplied from within this membrane. The protoplasm may in many instances readily supply the energy which creates the membrane gradients [cf. Brooks & Brooks (4, p. 171), who regard the protoplasm as the active seat of ion accumulation].

The intensity of the substance flux referred to unit conditions is termed the permeability constant having the dimension $cm.^{-2}$ $sec.^{-1}$ [cf., for instance, Brooks & Brooks (4, p. 9)]. It would be desirable if the presented permeability data, when possible, were expressed in this manner, because it would greatly facilitate comparisons between data collected on different objects and by different workers. One point has, however, to be strongly emphasized as to applying such a procedure to electrically charged particles be it ions or colloids; it is erroneous to define the unit driving force only by the concentration (or activity) gradient analytically found

or calculated. Such a procedure involves a tacit neglect of the electrical force, i.e., the influence of a simultaneously present difference of potential across the membrane, which must also be added (plus or minus!) to the force arising from the prevailing concentration difference. Neglect of this is rather common and may illustrate one source of the many discrepancies one may find when comparing quantitative data of the literature, particularly in determination of the well-known diffusion constant of Fick.

Permeability proper.—The mobility factor in the fundamental equation of flux given in the previous section corresponds physically to the reciprocal of the coefficient of the friction encountered by the permeating substance and can be expressed as velocity (under influence of the unit force). It is generally agreed upon that this mobility is a complex function of the nature of the penetrating particle, the solvent, the other solutes present, and the character of the membrane penetrated. The "mobility" would, from a theoretical point of view, be a clearer expression of the penetrability across a membrane than the "permeability constant" mentioned on p. 547.

By far the greatest amount of work in the permeability field has been devoted to solute-membrane behavior. Especially the role of membranes and cell and tissue boundaries have been in the focus of attention. However, many alleged characterizations of membranes in quantitative terms do not signify what the author meant, namely, a term describing the membrane. They are often just net figures of the amount of substance passing the membrane in question under the influence of undefined and perhaps changing driving forces.

The driving forces.—These can be of different nature and can operate simultaneously in superposition. This fact is seldom clearly understood. These forces in biological systems may be classified as follows:

(*a*) The thermodynamic gradient arises from a difference in chemical potential, which may be set as approximately proportional to the concentration difference, and is often described as "osmotic force." It acts on neutral molecules as well as on charged particles such as ions and colloids.

(*b*) Electrical potential gradients may be present in a membrane owing to simple or composite "diffusion," "membrane," or "phase boundary" potentials. These are recognized to exist in almost all tissue boundaries. In recent years they have been extensively

studied in connection with nerve conduction phenomena. The origin of these potentials is in general still largely obscure. Different authors favor different physical "explanations" and some, more or less in despair, speak in vague and general terms of "metabolism" and "chemical reactions" as sources of these potentials. Sometimes a reader gets the impression that the "physical" potentials (due to ionic diffusion, etc.) are regarded as incompatible with potentials which experimentally depend on some metabolic process, for instance, oxygen supply. This is not necessarily the case; any electric potential has some energy supply to which it owes its existence [cf. Lorente de Nó (5)]. This creates the inequalities of chemical potential of the ions or charged groups which ultimately come into play. Potentials obtained when inanimate membranes separate solutions of different electrolyte concentrations, may be artificially maintained by addition from external sources [see for instance (1, 3)]; in living material the same process can be accomplished by coupled chemical reactions. There is no difference in principle!

The electric potentials in cells and tissues may appear to have very modest values of some tens of millivolts, but it should be remembered that under the most favorable conditions the value of approximately fifty-eight millivolts can induce a tenfold separation of univalent charged particles. If maintained constant the electric potential π may "perform work" and drive the concentration ratio c_i/c_0 towards an equilibrium according to the following equation:

$$\text{electric work} = \text{osmotic work}$$

$$\epsilon \cdot F \cdot \pi \qquad RT \cdot 1n \frac{c_i}{c_0}$$

where ϵ is the charge (valency), R, T, and F the gas constant, the absolute temperature, and the Faraday, respectively. For particles in a colloidal state, which generally carry a "valency" greater than 1, one can anticipate quite marked unidirectional transportation effects from small potentials [cf. Teorell (6)]. It should be emphasized that the "electric work" according to the formula above does not imply that any current is flowing in the membrane nor can it alone lead to selective accumulation of one univalent cation (anion) in preference of another.

For transport processes under current flow the quantitative

effects upon ionic distribution may conform to the fundamental theories for moving boundary systems. The author has performed experiments on artificial systems which seem to corroborate this hypothesis (41, 42). Unfortunately no permeability implications of these concepts have as yet been described, although recent papers by Longsworth (7), Dole (8), and Svensson (9) seem to supply a good foundation for a treatment of this type of permeation. Here certainly is a field worthy of investigation. Some further aspects of the effect of current flow will be given on p. 561.

(*c*) Hydrostatic gradients play an eminent role in the animal body, where filtration or ultrafiltration occur, for instance, in the kidney glomeruli or the capillaries. This kind of force operates, however, solely on the solvent and a separation of the solutes is dependent on the characteristics both of the solute molecules, etc., and of the membrane supporting the gradient of solvent pressure. The quantitative definition of water permeation is given as a "filter constant" (cm.$\times$atm.$^{-1}\times$hr.$^{-1}$). Some interesting features relating to water transport have been recently discussed by Frey-Wyssling (cf. pp. 555–56).

In this connection it seems worth pointing out that most authors dealing with solute permeation and ionic accumulation, or ionic depletion, are not aware of the great possibilities of rather perplexing effects, which are inherent in the process called "diffusion against convention current," i.e., diffusion of solutes across a membrane, when the solvent also is subject to a movement. Theoretically this principle [employed in 1922 by Hertz (10, 11) for the separation of mixtures of gases having unequal diffusion rates] may lead to results of "selective permeation" [cf. Jacobs (12, p. 134)]. More work is apparently needed on this and related problems of simultaneous water transport (see pp. 551–52, 555–56). Electro-endosmotic phenomena are often very striking in model experiments, but their role in living membranes is far from clear and, in general, they lose significance when the salt concentration is as high as in animal tissues.

(*d*) Surface force gradients due to differences in surface, or rather, interfacial tension may be regarded as the two-dimensional counterparts to the osmotic forces in bulk. The phenomena of interfacial "diffusion" and "surface flow" strangely enough have not attracted the attention they deserve. Among more recent work is that of Crisp (13), which is especially worth mentioning.

One special feature of the transport in monolayers is that it may reach a high speed as compared with bulk transport. The friction encountered between the "surface dissolved," i.e., the adsorbed molecules, is probably often markedly lower in the state of a surface film than in bulk because such adsorbed molecules in a monolayer are more or less oriented. In such a proper array they are perhaps liable to glide along (under the influence of surface pressure gradients) with a greater ease than in bulk, where the orientation is at random [Gatty (14)]. One remarkable phenomenon which can accompany such surface spreading of oriented molecules is a considerable drag of water, called surface flow by Crisp (13) [cf. Schulman & Teorell (15)]. This may add to the scanty knowledge of factors determining water transport. Therefore, in this sector of permeability studies many blank spots have to be mapped in the future.

Physical Chemistry of Permeability

Diffusion, membrane effects, etc.—As has been pointed out earlier in this article the fundamentals of biological permeability ought to be more thoroughly studied by many of those who deal with its quantitative aspects. Fortunately there exists a number of excellent review articles written by experts. It might be worth mentioning Jacobs' outstanding treatise on diffusion (12). Of more recent date are the surveys by Longsworth (16) and by Harned (17), which can be recommended, the latter giving one hundred and eight references. Both deal mainly with electrolyte diffusion. Dean's excellent review (18) treats almost all aspects of membrane diffusion in aqueous systems; the chapter on active transport through membranes against concentration gradients is of special biological interest. Other papers by the same author supply new information of ionic diffusion (19, 20). Diffusion in narrow capillaries may meet with several special effects due to the increasing influence of the electric potentials residing in the wall layers; Davtyan (21) shows that such effects can severely affect the accuracy of the popular methods of measuring diffusion constants with the aid of porous membranes. Gordan (22) has also discussed a similar theme. Other complications in porous diffusion involving a reaction, or solution, in the solid pore walls have been offered as a possible mechanism of semipermeability by Petitpas & Mathieu (23). Important theoretical papers considering the

effect of hydrostatic pressure have been published by Bloch (24), and diffusion with discontinuous boundaries is treated by Hermans (25). Many phenomena displayed by living cell boundaries, in particular, electric properties relating to muscle and nerve membranes, are pictured by Höber (26, 27), the pioneer in this field.

Unequal concentration distributions across membranes have been demonstrated by various authors. Straub *et al.* (1) have repeated some old experiments of Straub on "harmony" distributions of electrolytes and have now found them to agree with theoretical equations on ionic accumulation developed by the reviewer (2, 3), where the electric force is taken into account. The theory of the Donnan effect [obtained as a special case of a "diffusion effect" in (2, 3)] has been extended by Deasy (28), who predicts unequal distributions also of nonelectrolytes. Osmotic pressure of colloids in membrane equilibrium is discussed by Chaudhury (29). Related movements of uncharged particles and molecules under current flow are the object of papers by Janssen (30) and by Longsworth (31), who have used the common electrophoresis technique. There seems to exist a special effect exerted directly on the solute molecules.

The possibility of marked separation effects simulating a "selective permeability" has been mentioned on pp. 549–50 in the discussion on "diffusion against convection current." Related to this topic are two recent papers of a physical character, which might be illuminating also for a biologist, one by Signer *et al.* (32) and the other by Kirillov (33). The first one demonstrates that a separation between sodium sulphate and sodium chloride can be achieved in a ratio 21:1. The latter paper contains a mathematical treatment of some experimental results.

Among other papers relating to the fundamentals of permeability may be mentioned a thermodynamic treatment of the movement of substance through a two-phase solution system [Broyer (34)]. It is shown that the basic principles for movement of solutes are analogous to those of water. Scatchard *et al.* (35) state that serum albumin in osmotic equilibrium with sodium chloride binds six molecules of chloride ions.

Surface phenomena.—The contribution of surface chemistry to the understanding of permeability seems to have been rather meager in recent years. The paper of Crisp (13) on two-dimen-

sional transport at fluid interfaces has already been mentioned (pp. 550–51). An article on surface-active agents in biology and medicine is written by Valkó (36).

Electrochemistry relating to permeability.—Here only some physical-chemical papers of interest will be discussed. Model experiments attempting to throw light on nerve action currents, especially as to the role of acetylcholine, are reviewed by Beutner & Barnes (37) [for biological implications concerning acetylcholine cf. Nachmansohn (38)]. Sollner & Gregor (39, 40) have continued their previous work on "permselective" collodion membranes with regard to the rate of establishment of the concentration potentials. It appears likely that experiments on these unique types of artificial membranes are capable of yielding a great deal of information on the mechanism of generation of electric potentials at charged, porous boundaries. Incidentally, the reviewer (41, 42) has also found them to be of excellent use in studies on the effects of flow of current (relating to problems of physiological electrotonus). In this connection the important papers by Longsworth (7), Dole (8), and Svensson (9) on moving boundary phenomena, which accompany flow of electric current in an electrolyte solution, may again be mentioned (cf. p. 550). In the opinion of the reviewer such phenomena localized on porous membranes can readily give rise to ionic redistribution effects, which may induce an analogy with rectification, and with capacity and inductivity in the electric sense [Teorell (42)].

Electro-capillarity phenomena are dealt with by Grahame (43) in a large review. Electro-osmosis as a source of anomalous osmosis, particularly in plant cells, has been studied by Brauner *et al.* (44, 45). Overbeek & Wijga (46) have confined their studies to diaphragms.

Cell and Tissue Permeability

Methods.—The outstanding tool for researches in permeability added in recent years is the radioactive "tracers" technique. A great mass of experimental data has emerged from the increasing supply of available radioelements, some of which will be discussed below in connection with the respective organs systems. Radiophosphorus has been especially popular, probably because it is fairly stable and easy to procure. As a quantitative tool for the study of permeability it is not an ideal substance, since in the

course of intermediary metabolism, it enters into a great many phosphorus compounds. Great caution is indeed necessary when interpreting data with tagged phosphorus as a "permeability indicator"!

The old "osmotic" methods, i.e., measurements of volume changes, are still favored by workers on cells and isolated organs. In competent hands they can yield reliable results, for example, Jacobs & Stewart (47), who have developed equations valid for work with red blood cells in complex external solutions. The uptake of glucose by brain slices has been measured by Elliott (48), leukocyte swelling and lysis by Tullis (49). An ingenious procedure of examining red blood corpuscles has been devised by Keilin & Hartree (50), who follow the penetration of substances forming methemoglobin by aid of microspectroscopy.

Permeability and metabolism.—In the general considerations of permeability forces (pp. 548–49) it has been emphasized, that any transport process must take place at the expense of energy, in inanimate as well as in animate systems. The manner in which this energy is supplied in living material is, in general, still concealed from us. Therefore, we have no reason to indicate a preference between a vitalistic and a purely physicochemical mechanism of permeability, a tendency which can often be traced even in modern work, and which is inherent in commonly used terms as "secretion" or "resorption." From a didactic point of view, however, an attempt to describe permeability in relation to metabolic processes, particularly in its dependence of oxygen, may be justified. A great number of such studies have been commented upon in previous volumes of this *Review.* Of recent papers Hunter's studies (51, 52, 53) on the penetration of nonelectrolytes in red blood cells may be cited as it demonstrates a case where the penetration does not seem to be related to aerobic or anaerobic metabolism. Other papers will appear below under different headings.

Ionic accumulation, etc.—This subject has been extensively treated in this *Review* in two recent articles (Vol. VII by S.C. Brooks, Vol. IX by Wilbrandt). As hardly any news of fundamental importance has emerged from the research during the period reviewed here, the reader is referred to the headings Erythrocytes, Muscle, etc., for information as to electrolyte distribution and to accompanying table. It may be concluded that the old problems termed "ionic accumulation," "selective ab-

sorption" or "preferential permeability," "secretion," "resorption," "excretion," etc., still challenge and puzzle the research worker. Some general aspects on these problems have been considered earlier in this article (p. 546).

TABLE I.

CELL AND TISSUE PERMEABILITY

Substance	Object	Conditions	Author(s)	Reference
Ferricyanide, Cu^{++}, etc.	Erythrocytes	—	Keilin & Hartree	50
Glycerol	"	Metabolism	Hunter	52
Glycerol, malonamide	"	—	Ørskov	58
Potassium-sodium exchange	"	Prolysis	Ponder	61, 62, 63
Potassium-sodium exchange	"	Cooling, pH	Maizels	69
Potassium loss	"	Lead poisoning	Ørskov	59
Sodium, potassium, chloride	"	Disease	Overman	70, 71
Chloride, carbon dioxide	"	Carbon dioxide, pH, etc.	Peters *et al.*	72, 74
Sodium, potassium	"	High gradients	Hald *et al.*	74
Phosphate, sulfate	"	External supply	Hald *et al.*	74
Glucose, salts	"	Insulin, sodium fluoride, etc.	Wilbrandt *et al.*	77
Estradiol	"	—	Bischoff & Katherman	78
Urea	"	—	Ørskov	58
Potassium loss	Muscle	Potassium free solution	Ivanoff & Scheiner	82
Radiosodium	"	Exchange	Ussing	83
Potassium-sodium exchange	"	—	Conway	81
Intracellular ions (inorganic)	"	—	Steinbach	80
Hydrochloric acid, alkali, chloride	Stomach	Exchange diffusion	Teorell; Öbrink	85, 86
Neutral red	"	Secretion rate	Öbrink	86
Various substances	Eye, etc.	—	Palm	97
Radiophosphate	"	—	Palm	105
Sugars	"	—	Davson & Duke-Elder	98
Radiosodium, etc.	"	—	Bárány	103
Radiosodium, -potassium, -calcium	Nerve axoplasm	—	Rothenberg & Feld	107
Radiophosphorus	Placenta	Pregnancy	Wilde *et al.*	110
Radiophosphorus	Placenta and erythrocytes	"	Naeslund & Nylin	111

Permeability to nonelectrolytes, dyes, etc.—The reader is referred to special headings of cell and tissue permeability below and to the attached table.

Water transfer.—The forces producing the steady streaming of water in living cells and tissues are yet far from clearly known, as has been emphasized in previous sections of this review (cf. pp. 550–51). Frey-Wyssling (54) has written an interesting article on the water permeability of the protoplasm. He develops formu-

lae for the permeation constant of water from the assumption that the permeation process is a counterdiffusion of dissolved molecules into the cell and water out of the (plant) cell (cf. pp. 549–50). A mechanism leading to secretion of water from cells is suggested by Osterhout (55), founded on experimentation with *Nitella*. A "suction potential" in relation to water permeability is discussed by Aykin (56). Membrane hardening and water intake in fish eggs are reported by Manery *et al.* (57). The discussion on the alleged existence of free and bound water has not yet come to an end; Ørskov (58, 59) working on lead poisoning of erythrocytes has found indication of bound water. Other papers on water exchange between cells and the environment can be found under headings Erythrocytes, etc., which follow.

Erythrocytes.—The structure and behavior of the erythrocyte membrane is still incompletely known. From Ponder's extended study has emerged the knowledge that the red cell envelope has a somewhat plastic or semielastic property since the shape of the cells can change reversibly from the normal disc-shape to a sphere under proper conditions. This process involves adsorption of certain surface active substances in competition with serum albumin [Ponder (60)]. Various substances having a lytic action can induce a prelytic loss of potassium from the cells, partly in exchange for sodium, without loss of hemoglobin (61, 62, 63). These experiments are contrary to the assumption that the mammalian red cells are generally impermeable to cations [see Hald *et al.* (64)]; they rather show that they are in a steady state with respect to their environment (cf. the comments on "false impermeability" on p. 546). A series of papers on hemolysis by Ponder (65, 66, 67) are worthy of mention, because such studies shed some light on the properties of the red cell membranes. Volume changes, lysis, and lysis-inhibition have been investigated in the presence of various agents such as anionic detergents, resorcinol, taurocholate, and saponin. For facts about the effects of pH, see the original papers. A method for the measurement of the osmotic fragility has been developed by Parpart *et al.* (68), who also analyses the effect of pH, temperature, and chemical environment.

Cation permeability can also be controlled by changes in temperature. Cooling to 7°C. causes the erythrocytes to lose potassium and gain sodium; warming to 37° activates glycolysis and the potassium-sodium movement is again reversed as confirmed by

Maizels (69), who now shows that this process is dependent on pH. Ørskov (59) finds potassium loss after lead treatment. Pathological aspects of cation permeability alterations are discussed by Overman (70, 71).

Anion permeability of the red cells is well-known, especially for carbonic acid, bicarbonate, and chloride. New studies by Peters *et al.* (72) have supplied more facts on the effect of carbon dioxide tension, pH, etc. It is reported that the red cell becomes more permeable to thiocyanate in the presence of histamine [Poli & Jucker (73)]. Another group in Peters' laboratory [Hald, Heinsen & Peters (74)] has performed a study on the distribution of electrolytes and water in human blood after addition of isotonic phosphates and sulfates. Only phosphate, associated with transfer of chloride and bicarbonate, enters the cells [cf. also Levi (75) and Delage (76)].

Nonelectrolytes have been the object of a few recent papers. Wilbrandt, Guensberg & Lauener (77) find that glucose entry into the human red cell is not affected by insulin, iodoacetate, or fluoride, although diminished by phloridzin. Increasing glucose concentration sharply decreases the permeability. Bischoff & Katherman (78) rightly point out that very little information is available as to the physicochemical status and distribution of steroid hormones. They demonstrate that estradiol freely permeates the red cell, a transfer governed solely by solubility conditions. The effects of urethane is reported by Robin *et al.* (79). The penetration of urea, glycerol, and malonamide is appreciable [Ørskov (59)].

Muscles.—An extensive review is recently published by Steinbach (80), where many references may be found. An interesting article by Conway (81) deals in particular with the movement of potassium and sodium and its possible nature. It is a well-established fact that the potassium accumulation in muscles is quite high and it is generally regarded that this elevated potassium concentration is a necessary condition for normal contractility. Ivanoff & Scheiner (82) report, however, that as much as 70 per cent may be lost in the isolated frog gastrocnemius muscle before the electric excitability ceases. The exchange of radiosodium in frog sartoriae after equilibration has been found quite rapid, a fact commented upon by Ussing (83).

Stomach.—The gastric mucosa exhibits one of the most remarkable ionic accumulation phenomena found in living tissues,

since it produces more than tenth normal hydrochloric acid against a concentration gradient of the order of one million! Because this is a prototype of a secretion problem the relevant papers will be dealt with at some length. Linde, Teorell & Öbrink (84) describe experiments, which indicate that the "primary acidity" may be as high as 350 m.eq./l., which is about double the customarily accepted value. The "secondary acidity," i.e., that of the collected gastric juice, is in general well below 0.17 normal and is variable with the volume rate of the acid secretion. The mechanism of this so-called acidity regulation has for many decades been a matter of argument in stomach physiology. The reviewer (85) has recently advanced a quantitative hypothesis for the acidity variations in terms of exchange diffusion between hydrochloric acid of the gastric content and alkali chlorides of the mucosa or blood. It appears to fit well with experimental data on human beings and animals. Öbrink (86) has also treated a number of other permeability problems of the stomach. He suggests that the chloride accumulation of the gastric juice (about 50 per cent above that of the blood plasma) is caused by the interference of carbonic anhydrase, which decomposes bicarbonate ions thus favoring chloride ions (86, pp. 70–79). The same author has also examined quantitatively the excretion of the dye neutral red, which seems to be closely connected with the acid formation.

The fundamental problem of the mechanism of accumulation of hydrogen ions has attracted considerable attention in recent years. Conway & Brady (87, 88) once more point out the possible bearing of acid formation by yeast cells on the problem of gastric acidity. Their theory involves essentially an exchange reaction of potassium against hydrogen ions emanating from organic acids. Quite a different approach is met with in reports by Davies and his collaborators (89, 92, 93) working on isolated frog mucosa. Davies (89) found that secretion was accompanied by an increased over-all uptake of oxygen with a simultaneous production of bicarbonate. This finding has been substantiated by experiments at different temperatures by the reviewer [Teorell (90)]. Following old leads recently revived by Rehm [see Rehm & Hokin for references (91)], Davies *et al.* (92, 93) incorporate the electrical potential difference of the mucosa (of some ten millivolts) in a theory for the mechanism of formation of the hydrochloric acid. They claim that there exists a covariation between potential difference

and secretion intensity, which could be enhanced or inhibited by current flow externally applied. However, the reviewer, in collaboration with Wersäll (94), in an independent series of similar experiments, could not obtain evidence of such regular parallelism between potential difference and secretion. Even when the secretion periods were extended over many hours under well controlled temperature conditions the interrelation was still obscure (95). Further discussions on factors influencing the electric potentials of the gastric mucosa will be found in Rice & Ross' paper (96).

Eye, cerebrospinal fluid, and the nervous system.—There seems to be no agreement as yet as to the mechanisms underlying the distribution and transfer of various substances in the eye fluids. One group of authors adheres to a dialysis or ultrafiltration theory, while another leans towards active secretion concepts. A brief survey in these problems is given by Palm (97). Davson & Duke-Elder (98), both known from earlier work in this field, have recently examined the rate of penetration of various sugars into the intraocular fluids and found them to be rapid in comparison with that of analogous, lipoid-insoluble molecules diffusing into plant cells. A series of papers relating to the regulation of the intraocular pressure have been written by Bárány (99, 100, 101). With various methods he has attempted to elucidate the problems of aqueous transfer and the dynamics of the intraocular pressure. Vapor pressure determinations (102), as well as experiments with radiosodium (103), yielded results, which Bárány attributes to the existence of secretion mechanisms. The permeation of radioelements has also been studied by Wang (104), who employed radiosodium and radiochloride. Palm (105) has performed thorough studies on the exchange of labelled phosphate (P^{32}) between the blood and different parts of the eye, via the anterior uvea and the aqueous humor to the lens. The significance of the differences in the rate of turnover observed is discussed. Finally may be mentioned a paper by Holt & Cogan (106), who attempt to determine the permeability of the excised cornea by impedance measurements.

In a short communication Rothenberg & Feld (107) describe the penetration of radioactive potassium, sodium, and calcium into the giant nerve axoplasm of squid. Only potassium was accumulated (to almost twice the outside concentration) indicating an "active process."

Skin, placenta.—An extensive review on metabolism and permeability of the skin was recently published by Calvery, Draize & Lang (108) to which the reader is referred. In general it may said that the skin can appear permeable for lipoid-soluble substances [cf. Frommel *et al.* (109)].

The placenta has been studied by Wilde *et al.* (110), who found that labelled phosphorus permeated more readily towards the end of pregnancy. The possibility of transfer of particles as large as erythrocytes from the mother to the fetus is indicated by some experiments by Naeslund & Nylin (111) and by Hedenstedt & Naeslund (112), using infusion of normal blood cells tagged with radiophosphorus and elliptic red cells (elliptocytes), respectively.

Blood capillaries and lymphatics.—These topics are reviewed in other chapters in this volume (see Peripheral Circulation and Lymphatic System) and are therefore omitted here. A paper by Landis (113) and one by Chambers & Zweifach (114) give good surveys of important facts.

Bioelectric work.—The major part of recent work in these branches of permeability research falls under the heading "Bioelectric Potentials in the Nervous System and Muscle," which is treated by another reviewer in this volume. Here only some comments will be made as to two methods of measuring ionic permeability, which are electric in nature, namely (*a*) determination of ionic mobilities from potential measurements, and (*b*) determination of the conductivity (impedance) with direct or alternating current as a means of characterizing cell or membrane properties. Both are founded on the correct assumption that the potential and conductivity are functions, *inter alia*, of the ionic mobilities.

(*a*) The well-known Nernst-Planck formulae for a "concentration potential" (between two concentrations of a binaryelectrolyte) and for the "chemical" potential (between two different species of electrolytes of the same concentration) are often used for calculations of ionic mobilities. The presence of a porous, convection proof membrane between the solutions does not invalidate the simple formulae, provided the membrane is neutral. If, however, the membrane carries an electric charge (due to its acid, basic, or ampholytic character) severe deviations from the formulae will become increasingly evident with decreasing concentrations of the electrolyte solutions under test. This peculiar effect, displayed at charged membranes, has for long been known as the "concentra-

tion effect," implying that the potential contrary to the predictions from the Nernst formula, is dependent on the absolute values of the electrolyte concentrations (instead of their ratio). A first attempt to extend this formula, in terms of mobility and concentrations, to include also the influence of the membrane "charge" was made by the reviewer (115) and, somewhat later, by Meyer & Sievers (116). An analysis of the new formulae shows that within the membrane from the potentials by the use of the simple Nernst-Planck formulae, neglecting the membrane charge, one cannot determine the ionic mobilities as has been attempted in many quarters.

(*b*) As regards the impedance method with alternating currents it may be said that it is a rather convenient way of determining "something" related to the membrane or tissue permeability. This method has been brought to some degree of perfection in performance in recent years, especially by Cole and his collaborators (117, 118), but the interpretation of the results, commonly presented as "impedance loci diagrams," and their real significance in relation to the living structures, is not easy. Rapid impedance changes, often displayed by tissues, may be handled by aid of "square wave analysis" [Teorell (119, 120)]. Studies by aid of this method (42, 120) on artificial membranes (porous glass, cellophane, etc.) have opened a possibility of explaining, at least in some instances, the appearance of capacity and inductivity effects in living tissues [cf. work by Cole *et al.* (117, 118)] in terms of ionic distribution subject to current flow (cf. the comments on p. 553). It is hoped that studies with models of this type will help clarify the term "polarization" so ambiguously used in physiology.

Finally, attention should be called to experimenters dealing with the technique of impedance measurement: Blank & Finesinger (121), who have been interested in skin measurements, and Rothschild (122), who studied impedance variations in salmon eggs.

LITERATURE CITED

1. Straub, J., van Eijk, M., Wilde, J. H., and Hekker, T., *Rec. trav. chim.*, **65**, 545–48 (1946)
2. Teorell, T., *Proc. Natl. Acad. Sci. U.S.*, **21**, 152–61 (1935)
3. Teorell, T., *J. Gen. Physiol.*, **21**, 107–22 (1937)
4. Brooks, S. C., and Brooks, M. M., *The Permeability of Living Cells*, **19**, 392 pp. (Protoplasma-Monographien, Berlin, 1941)
5. Lorente de Nó, R., *Harvey Lectures*, Ser. **62**, 43–105 (1946–47)

6. TEORELL, T., *Trans. Faraday Soc.*, **33**, 939–41, (1937)
7. LONGSWORTH, L. G., *J. Am. Chem. Soc.*, **67**, 1109–19 (1945)
8. DOLE, V. P., *J. Am. Chem. Soc.*, **67**, 1119–26 (1945)
9. SVENSSON, H., *Arkiv. Kemi, Mineral. Geol.* [A]**22**, 1–154 (1946)
10. HERTZ, G., *Physik. Z.*, **23**, 433–34 (1922)
11. HERTZ, G., *Z. Physik*, **19**, 35–42 (1923)
12. JACOBS, M. H., *Ergeb. Biol.*, **12**, 1–160 (1935)
13. CRISP, D. J., *Trans. Faraday Soc.*, **46**, 619–35 (1946)
14. GATTY, O., *Trans. Faraday Soc.*, **33**, 341 (1937)
15. SCHULMAN, J. H., AND TEORELL, T., *Trans. Faraday Soc.*, **34**, 1337–42 (1938)
16. LONGSWORTH, L. G., *Ann. N. Y. Acad. Sci.*, **46**, 211–39 (1945)
17. HARNED, H. S., *Chem. Revs.*, **40**, 461–522 (1947)
18. DEAN, R. B., *Chem. Revs.*, **41**, 503–23 (1947)
19. DEAN, R. B., *J. Am. Chem. Soc.*, **67**, 31–35 (1945)
20. DEAN, R. B., AND LORING, H. S., *J. Biol. Chem.*, **157**, 717–21 (1945)
21. DAVTYAN, O. K., *J. Phys. Chem.* (*U.S.S.R.*), **20**, 1043–47 (1946)
22. GORDON, A. R., *Ann. N. Y. Acad. Sci.*, **46**, 285–308 (1945)
23. PETITPAS, T., AND MATHIEU, M., *Compt. rend.*, **222**, 1486–88 (1946)
24. BLOCH, I., *Bull. Math. Biophys.*, **9**, 63–74, (1947)
25. HERMANS, J. J., *J. Colloid Sci.*, **2**, 387–98 (1947)
26. HÖBER, R., *Ann. N. Y. Acad. Sci.*, **47**, 381–94 (1946)
27. HÖBER, R., *Physical Chemistry of Cells and Tissues*, 676 pp. (The Blakiston Co., Philadelphia, Pa., 1944)
28. DEASY, C. L., *Science*, **104**, 388–89 (1946)
29. CHAUDHURY, S. G., *J. Phys. Chem.*, **50**, 486–88 (1946)
30. JANSSEN, L. W., *Rec. trav. chim.*, **65**, 564–70 (1946)
31. LONGSWORTH, L. G., *J. Am. Chem. Soc.*, **69**, 1288–91 (1947)
32. SIGNER, I. R., HÄNNI, H., KOESTLER, W., ROTTENBERG, W., AND VON TAVEL, P., *Helv. Chim. Acta*, **29**, 1984–91 (1946)
33. KIRILLOV, N. I., *J. Applied Chem.* (*U.S.S.R.*), **18**, 381–92 (1945)
34. BROYER, T. C., *Science*, **105**, 67–69 (1947)
35. SCATCHARD, G., BATCHELDER, A. C., AND BROWN, A., *J. Am. Chem. Soc.*, **68**, 2320–29 (1946)
36. VALKÓ, E. I., *Ann. N. Y. Acad. Sci.*, **46**, 451–78 (1946)
37. BEUTNER, R., AND BARNES, T. C., *Biodynamica*, **5**, 117–28 (1945)
38. NACHMANSOHN, D., *Ann. N. Y. Acad. Sci.*, **47**, 395–428 (1946)
39. SOLLNER, K., AND GREGOR, H. P., *J. Phys. Chem.*, **50**, 470–76 (1946)
40. SOLLNER, K., AND GREGOR, H. P., *J. Phys. & Colloid Chem.*, **51**, 299–311, (1947)
41. TEORELL, T., *Abstracts Intern. Physiol. Congr., 17th Congr., Oxford*, 252 (1947)
42. TEORELL, T., *Nature* (In press)
43. GRAHAME, D. C., *Chem. Revs.*, **41**, 441–501 (1947)
44. BRAUNER, L., *Rev. faculté sci. univ. Istanbul* [B]**10**, 1–59 (1945)
45. BRAUNER, L., AND HASMAN, M., *Rev. faculté sci. univ. Istanbul* [B]**12**, 210–54 (1947)
46. OVERBEEK, J. TH. G., AND WIJGA, P. W. O., *Rec. trav. chim.*, **65**, 556–63 (1946)
47. JACOBS, M. H., AND STEWART, D. R., *J. Cellular Comp. Physiol.*, **30**, 79–103 (1947)

48. ELLIOTT, K. A. C., *Proc. Soc. Exptl. Biol. Med.*, **63**, 234–36 (1946)
49. TULLIS, J. L., *Am. J. Physiol.*, **148**, 708–14 (1947)
50. KEILIN, D., AND HARTREE, E. F., *Nature*, **157**, 210–13 (1946)
51. HUNTER, F. R., *J. Cellular Comp. Physiol.*, **29**, 301–12 (1947)
52. HUNTER, F. R., *J. Cellular Comp. Physiol.*, **29**, 313–21 (1947)
53. HUNTER, F. R., AND HUNTER, M. K., *Proc. Oklahoma Acad. Sci.*, **27**, 21–24 (1947)
54. FREY-WYSSLING, A., *Experientia*, **2**, 132–37 (1946)
55. OSTERHOUT, W. J. V., *J. Gen. Physiol.*, **30**, 439–47 (1947)
56. AYKIN, S., *Rev. faculté Sci. Univ. Istanbul* [B]**11**, 273–95 (1946)
57. MANERY, F. J., FISHER, K. C., AND MOORE, E., *Rev. can. biol.*, **6**, 169, (1947)
58. ØRSKOV, S. L., *Acta Physiol. Scand.*, **12**, 192–201 (1946)
59. ØRSKOV, S. L., *Acta Physiol. Scand.*, **12**, 202–12 (1946)
60. PONDER, E., *J. Exptl. Biol.*, **23**, 350–56 (1947)
61. PONDER, E., *J. Gen. Physiol.*, **30**, 235–46 (1947)
62. PONDER, E., *J. Gen. Physiol.*, **30**, 379–87 (1947)
63. PONDER, E. *J. Gen. Physiol.*, **30**, 479–91 (1947)
64. HALD, P. M., TULIN, M., DANOWSKI, T. S., LAVIETES, P. H., AND PETERS, J. P., *Am. J. Physiol.*, **149**, 340–49 (1947)
65. PONDER, E., *J. Gen. Physiol.*, **29**, 203–18 (1946)
66. PONDER, E., *J. Gen. Physiol.*, **30**, 15–23 (1946)
67. PONDER, E., *J. Gen. Physiol.*, **31**, 325–35 (1948)
68. PARPART, A. K., LORENZ, P. B., PARPART, E., GREGG, J. R., AND AURIN, M. C., *J. Clin. Invest.*, **26**, 636–40 (1947)
69. MAIZELS, M., *J. Physiol.* (*London*), **107**, 9 P–10 P (1948)
70. OVERMAN, R. R., *J. Lab. Clin. Med.*, **31**, 1170–73 (1946)
71. OVERMAN, R. R., *Am. J. Physiol.*, **152**, 113–21 (1948)
72. PETERS, J. P., TULIN, M., DANOWSKI, T. S., AND HALD, P. M., *Am. J. Physiol.*, **148**, 568–81 (1947)
73. POLI, E. AND JUCKER, S., *Boll. soc. ital. biol. sper.*, **21**, 33–34 (1946)
74. HALD, P. M., HEINSEN, A. J., AND PETERS, J. P., *Am. J. Physiol.*, **152**, 77–85 (1948)
75. LEVI, M., *Boll. soc. ital. biol. sper.*, **23**, 633–35 (1947)
76. DELAGE, B., *Compt. rend.*, **225**, 1187–88 (1947)
77. WILBRANDT, W., GUENSBERG, E., AND LAUENER, H., *Helv. Physiol. et Pharmacol. Acta*, **5**, C20–22 (1947)
78. BISCHOFF, F., AND KATHERMAN, R. E., *Am. J. Physiol.*, **152**, 189–96 (1948)
79. ROBIN, E. D., DURY A., ESSMAN, L., AND LEESE, CH.E., *Federation Proc.*, **6**, 190 (1947)
80. STEINBACH, H. B., *Ann. N. Y. Acad. Sci.*, **47**, 849–74 (1947)
81. CONWAY, E. J., *Nature*, **157**, 715–17 (1946)
82. IVANOFF, N., AND SCHEINER, H., *Compt. rend. soc. biol.*, **140**, 250–52 (1946)
83. USSING, H. H., *Nature*, **160**, 262–63 (1947)
84. LINDE, S., TEORELL, T., AND ÖBRINK, K. J., *Acta Physiol. Scand.*, **14**, 220–32 (1947)
85. TEORELL, T., *Gastroenterology*, **9**, 425–43 (1947)
86. ÖBRINK, K. J., *Acta Physiol. Scand.*, **15**, Suppl. No. 51, 1–106 (1948)
87. CONWAY, E. J., AND BRADY, T. G., *Nature*, **159**, 137–38 (1947)

88. CONWAY, E. J., AND BRADY, T. G., *Nature*, **159**, 876–77 (1947)
89. DAVIES, R. E., *Biochem. J.*, **40**, xxxv (1946)
90. TEORELL, T., *Experientia* (In press)
91. REHM, W. S., AND HOKIN, L. E., *Am. J. Physiol.*, **149**, 162–76 (1947)
92. DAVIES, R. E., LONGMUIR, N. M., AND CRANE, E. E., *Biochem. J.*, **40**, xxxvi (1946)
93. DAVIES, R. E., LONGMUIR, N. M., AND CRANE, E. E., *Nature*, **159**, 468–69 (1947)
94. TEORELL, T., AND WERSÄLL, R., *Acta Physiol. Scand.*, **10**, 243–57 (1945)
95. TEORELL, T., *Acta Physiol. Scand.* (In press)
96. RICE, H. V., AND ROSS, R. T., *Am. J. Physiol.*, **149**, 77–94 (1947)
97. PALM, E., *Acta Ophthalmol.*, **24**, 189–98 (1946)
98. DAVSON, H., AND DUKE-ELDER, W. S., *J. Physiol. (London)*, **107**, 141–52 (1948)
99. BÁRÁNY, E. H., *Nature*, **158**, 665 (1946)
100. BÁRÁNY, E. H., *Acta Physiol. Scand.*, **13**, 95–102 (1947)
101. BÁRÁNY, E. H., *Brit. J. Ophthalmol.*, **31**, 160–76 (1947)
102. BÁRÁNY, E. H., *Acta Physiol. Scand.*, **13**, 81–86 (1947)
103. BÁRÁNY, E. H., *Acta Physiol. Scand.*, **13**, 55–61 (1947)
104. WANG, J.-C., *J. Gen. Physiol.*, **31**, 259–68 (1948)
105. PALM, E., *Acta Ophthalmol.*, Suppl. No. 32, 189 (1948)
106. HOLT, M., AND COGAN, D. G., *Arch. Ophthalmol.*, **35**, 292–98 (1946)
107. ROTHENBERG, M. A., AND FELD, E. A., *J. Biol. Chem.*, **172**, 345–46 (1948)
108. CALVERY, H. O., DRAIZE, J. H., AND LANG, E. P., *Physiol. Revs.*, **26**, 495–540 (1946)
109. FROMMEL, E., BISCHLER, A., GOLD, P., AND BISCHLER, V., *Helv. Physiol. et Pharmacol. Acta*, **4**, C43–4 (1946)
110. WILDE, W. S., COWIE, D. B., AND FLEXNER, L. B., *Am. J. Physiol.*, **147**, 360–69 (1946)
111. NAESLUND, J., AND NYLIN, G., *Acta Med. Scand.*, Suppl. No. 170, 390–98 (1946)
112. HEDENSTEDT, S., AND NAESLUND, J., *Acta Med. Scand.*, Suppl. No. 170, 126–34 (1946)
113. LANDIS, E. M., *Ann. N. Y. Acad. Sci.*, **46**, 713–31 (1946)
114. CHAMBERS, R., AND ZWEIFACH, B. W., *Physiol. Revs.*, **27**, 436–63 (1947)
115. TEORELL, T., *Proc. Soc. Exptl. Biol. Med.*, **33**, 282–85 (1935)
116. MEYER, K. H., AND SIEVERS, J. F., *Helv. Chim. Acta*, **19**, 649–77 (1936)
117. COLE, K. S., AND BAKER, R. F., *J. Gen. Physiol.*, **24**, 771–88 (1941)
118. COLE, K. S., *J. Gen. Physiol.*, **25**, 29–51 (1941)
119. TEORELL, T., *Acta Physiol. Scand.*, **12**, 235–54 (1946)
120. TEORELL, T., *Acta Physiol. Scand.*, **16**, Suppl. No. 53, 62 (1948)
121. BLANK, I. H., AND FINESINGER, J. E., *Arch. Neurol. Psychiat.*, **56**, 544–57 (1946)
122. ROTHSCHILD, LORD, *Nature*, **159**, 4030, 134–5 (1947)

PHARMACOLOGY

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The present review summarizes work published in 1947 and up to July, 1948 on certain aspects of autonomic nervous system pharmacology and on the newer synthetic analgesic drugs.

AUTONOMIC NERVOUS SYSTEM PHARMACOLOGY

Since a complete and critical review of all the work on "autonomic" drugs would exceed the space allotted, emphasis has been placed on ganglionic blocking agents, adrenergic blocking agents, and central impairment of sympathetic reflex pathways.

Ganglionic Blocking Agents

Tetraethylammonium.—A renewed interest in compounds capable of interrupting synaptic transmission in autonomic ganglia has been aroused by the reinvestigation of the properties of the tetraethylammonium ion (T.E.A.). This compound has long been known to be exceptional in the series of simple ammonium salts for its lack of muscarinic and curariform actions (1, 2). It has been shown to inhibit the pressor actions of tetramethylammonium salts (3), an action presumably due to an action on sympathetic ganglia. Acheson & Moe and Acheson & Pereira studied its effects on the mammalian heart, on which it exerts a positive inotropic action (4), on the mammalian circulation, where it affects heart rate and blood pressure demonstrably due to interruption of transmission in autonomic ganglia (5), and on transmission in the superior cervical sympathetic ganglion of the cat (6). The drug prevents the response of the nictitating membrane to preganglionic, but not to postganglionic, stimulation and, like curare, prevents the response to acetylcholine, but not to potassium chloride, injected into the ganglion (6). The lack of other actions, particularly of a curariform nature, has been emphasized; large doses injected intra-arterially increase the twitch height of the cat's calf muscles in response to sciatic nerve stimulation, and even restore the response of the partially curarized muscle. Depression of the response to nerve stimulation or injected acetylcholine occurs only after repeated doses (7). In dogs under anesthesia infusion of T.E.A.

at a high rate produces death by respiratory paralysis; at the time of respiratory failure skeletal muscles still respond to nerve stimulation (8). If infusion is continued, muscular fasciculation appears; eventually fasciculation stops, and at this time nerve stimulation no longer arouses contraction of muscles (8). An attempt has been made to explain the lack of curariform activity as compared with other simple quaternary salts in terms of the "charge-distributing" effect of the ethyl radicals. Curariform activity is said to be related to the concentration of the ionic charge on the central nitrogen atoms (9). Although subjective symptoms of weakness have been described in the human subject (10, 11), these are almost certainly not curariform. Unanesthetized rabbits and mice die in convulsions, probably asphyxial (8). Choline, which has been shown to protect mice against the lethal effects of the triethyl analogue of choline (13), also raises the acute LD_{50} of T.E.A. (8). The mechanism has not been elucidated. The drug apparently causes no sign indicative of chronic intoxication. Animals which recover from acute effects survive without evidence of pathological change (12).

The unique pharmacological action of T.E.A. and its relative freedom from other effects (muscarinic, curariform, etc.) have led to its extensive use as a tool in the study of autonomic regulations. In the human subject it produces postural hypotension, vasodilation of the extremities, cardioacceleration, paralysis of visual accommodation, inhibition of secretion of salivary, gastric, and sweat glands, and inhibition of the smooth muscle of the gut and bladder (11). Mean arterial pressure is reduced slightly in normotensive (14) and significantly in most hypertensive subjects (15), suggesting a neurogenic component in essential hypertension. Variation in the day-by-day depressor response in hypertensive subjects has been proposed as evidence of a varying humoral component (16). The drug has, however, proved only moderately useful in predicting the response to extensive sympathectomy in hypertension (10, 15, 17). Although the drug causes a marked depressor response in neurogenic hypertension in dogs, it causes little action in either early or late experimental renal hypertension (18). No therapeutic use is claimed for the drug in hypertension, although relief of hypertensive headache (15) and temporary improvement in hypertensive heart failure have been reported (17).

T.E.A. produces vasodilatation in areas under sympathetic vasoconstrictor control, particularly in the feet, as evidenced by

skin temperature and venous occclusion plethysmographic studies in human subjects (19 to 22). The magnitude of this response is less than that produced by successful sympathetic block or spinal anesthesia, probably because clinical doses do not produce complete interruption of vasomotor paths (19, 20, 21); the response is said by some to be too unpredictable to yield information of value about the relative role of neurogenic constriction in peripheral vascular disease (23, 24), but T.E.A. has been successfully applied to the diagnosis and treatment of peripheral vascular disease (25, 26, 27). It blocks the neurogenic vasospasm induced by the cold pressor stimulus (28) and the cardiovascular collapse induced by stimulation of the hyperactive carotid sinus (29). Vasodilatation in the extremities depends, of course, on an intact nerve supply. No dilator response occurs in sympathectomized extremities (27). A decrease in renal resistance occurs in some individuals, as evidenced by maintained *p*-aminohippurate clearance in the presence of a decreased arterial pressure (30).

Although T.E.A. produces striking inhibition of gastrointestinal motility in normal human subjects (31, 32), the mechanism of this inhibition cannot be clearly assigned to ganglionic inhibition (33). T.E.A. has no clear-cut action on isolated rabbit ileum (34), and although it produces inhibition of the small intestine in the unanesthetized dog, the degree of inhibition is less than in human subjects and, like the inhibitory actions of epinephrine and atropine, is more pronounced on a denervated Thiry-Vella loop than on the innervated bowel (35). T.E.A. does not block the motor effect of vagal stimulation on the duodenum (36, 37). T.E.A. is said to enhance the response of the isolated guinea pig ileum to angiotonin and histamine, but not usually to acetylcholine or barium chloride (38).

Gastric secretion is depressed in volume and in concentration of acid in normal subjects and in ulcer patients (33, 39). Pain relief is believed to be due to inhibition of motility rather than reduction of acid secretion (31). T.E.A. is said to prolong the survival and reduce the incidence of ulcers in Shay rats (pyloric ligation) (40).

Inhibition of bladder motility has been reported in human subjects by Nesbit and co-workers (41) and in cats by Root (42), but the drug apparently has no action on the human ureters [Lapides (43)].

The use of T.E.A. in the study of vasomotor reflexes has been

reported in preliminary studies. The drug blocks the reflex hypertension resulting from carotid occlusion or central vagal stimulation but does not prevent the direct action of pressor agents such as epinephrine or angiotonin (44, 52). It potentiates the blood pressure effects of nitroglycerine, hemorrhage, plethora, and epinephrine (44), restores the pressor action of renin in animals in which tachyphylaxis has developed (45), and potentiates the renal blood flow actions of epinephrine and "Isuprel" (46). Destruction of the spinal cord prevents T.E.A. potentiation of epinephrine and the renal pressor agents (47). The observation of epinephrine potentiation provoked the statement that this drug should not be used to overcome vascular collapse induced by T.E.A. in human subjects (48). It has been emphasized that an agent which interrupts autonomic pathways should be expected to enhance both pressor and depressor responses to drugs (49). T.E.A. does not block the pressor response to asphyxia in dogs, although purely adrenolytic agents do (50). It is possible that anoxia produces a direct, as well as a neuroegnic, excitation of the adrenal medulla (51).

Although it has been reported that T.E.A. has a direct vasodilator action (53) this is probably in error, for direct injection into the femoral artery of dogs produces, if any action, only vasoconstriction (5).

T.E.A. has no obvious direct action on carotid chemoreceptors (53), but it does prevent the hyperpneic response to acetylcholine, nicotine, and lobeline in the atropinized dog [Moe *et al.* (54)]. Since it does not prevent the response to cyanide, the block must be in the chemoreceptor organ rather than central. T.E.A. does not prevent the hyperpneic response to hypoxia; the respiratory depression produced by large doses is believed to be central. There is no apparent interference with afferent stretch receptor mechanisms (54).

Although preliminary attempts to demonstrate by means of T.E.A. a role of nervous regulation in the control of blood sugar have been largely fruitless (55), the drug has been reported to prevent the hyperglycemic response to morphine (56).

Neostigmine has been proposed as an antidote to T.E.A. and has been shown to antagonize various actions of the drug in both animal and human subjects [Reardon *et al.* (57)]. Since T.E.A. probably blocks ganglia by competition with acetylcholine, any

cholinesterase inhibitor should be capable of overcoming the blockade.

Excretion of T.E.A. is accomplished by the kidney by both glomerular filtration and tubular excretion [Rennick *et al.* (58)]. Some reabsorption may occur, but clearance of the drug is rapid in the dog and in man.

Other compounds with ganglionic blocking action.—Blockade of ganglia is a more common property of quaternary ammonium salts than previously recognized, although many compounds possess other actions as well (muscarinic, curariform, atropine-like, etc.). Congeners of T.E.A. have been studied by Acheson (59) and by Freyburger & Moe (60). A series of four bistriethylammonium compounds were studied by Chou & de Elio (61). Ethylene-bistriethylammonium, as tested on the perfused superior cervical ganglia of the cat, was one-third as active as T.E.A.; the triethylene and pentamethylene compounds were quite inactive, and the decamethylene homologue was twice as active as T.E.A. The inhibitory action of epinephrine on ganglionic transmission has been re-emphasized by Marrazzi & Marrazzi (62), who describe a post-inhibitory facilitation believed to account for the contrary conclusions of Bülbring (63). The magnesium ion also depresses ganglionic transmission, but unlike T.E.A. prevents the ganglionic response to potassium as well as to acetylcholine [Stanbury (64)]. A primary ganglionic depressant activity has also been observed with 2, 3- and 2, 4-dimethylpiperidines [Koppanyi & Vivino (65)]. Nicotine, like T.E.A., has little action on synaptic transmission in the mammalian spinal cord (66), but produces facilitation and depression in a central nervous system synapse of the crayfish. The response of this structure to most autonomic drugs differs from that of ganglionic synapses in mammals (67).

Adrenolytic Agents

Since the demonstration of effective antagonism of motor actions of epinephrine by dibenzyl-β-chloroethylamine (dibenamine) and related compounds by Nickerson & Goodman (68) much interest has developed in adrenolytic compounds as pharmacological tools and as possible therapeutic agents. Dibenamine (and many closely related substances) blocks motor actions of epinephrine but is less effective against sympathetic nerve stimulation (69). It

does not facilitate destruction of epinephrine and is said not to prevent penetration into the effector cell. It does not prevent motor actions of other, nonsympathomimetic, smooth muscle stimulants. The site of action is believed to be in the smooth muscle cell, and the difference between effects on epinephrine and nerve stimulation are referrred to a possible difference of anatomic accessibility (69). Comparing pressor dose-response curves to epinephrine and norepinephrine under various conditions it has been found that pressor actions of these two agents are depressed to an equal degree by a dose of dibenamine in the pithed cat (in which epinephrine rarely induces a depressor response), while in the anesthetized (nonpithed) dog the pressor response to epinephrine is replaced by a depressor response after doses of dibenamine which only moderately reduce the pressor response to norepinephrine (70). It was also found that the pressor response to carotid clamping persisted until sufficient dibenamine had been administered to abolish almost entirely the pressor action of norepinephrine. This observation suggests that the difference between epinephrine and sympathetic nerve stimulation may be merely the result of a depressor component of the former which by algebraic summation cancels out the pressor response.

The sympatholytic action of dibenamine has been confirmed by other workers (71, 72, 73). As expected, it prevents the vasoconstrictor action of epinephrine in the frog hind-leg preparation, although it fails to prevent the effects of angiotonin or nicotine (74). In renal hypertensive dogs the drug produces no markedly greater depressor response, either early or late, than in normal animals (18) and causes no sustained fall in pressure even after repeated injection (75). In cases of moderate essential hypertension in human subjects, the drug induces a fall of pressure to near-normal levels and causes postural hypotension for twenty-four to seventy-two hours after a single dose of 5 mg. per kg. (76). No depressor response occurs in malignant hypertension, possibly indicating a direct role of a renal humoral agent in such cases.

Dibenamine does not prevent the positive inotropic and chronotropic actions of epinephrine on the mammalian heart; large doses exert a negative inotropic action and reduce the rate at which rabbit auricles will respond to electrical stimulation (quinidine-like action) [Acheson, Farah & French (77)]. It does not prevent reflex cardioacceleration induced by depressor drugs, nor reflex brady-

cardia induced by "pitressin" or angiotonin (78). In spite of the apparent lack of adrenolytic actions in the heart, dibenamine effectively prevents the induction of ventricular tachycardia and fibrillation by epinephrine in animals under cyclopropane anesthesia. The protection is said not to be due to reversal of pressor actions of epinephrine, nor to interference with a vagal reflex, nor to a quinidine-like action of dibenamine (79), but evidence has been advanced that ventricular tachycardia, though probably not fibrillation, can be induced in the presence of dibenamine by producing a sufficient elevation of pressure immediately after injection of epinephrine (80).

Central nervous system excitation occurs as a side effect with rapid administration of dibenamine (73); in addition, a toxic effect on the kidney, evidenced by impaired excretion of *p*-aminohippurate, has been described in the dog (81). No evidence of renal damage has developed, however, in studies on human subjects (82).

Dibenamie reverses the anticurare action of epinephrine, but not that of potassium, an observation which suggests that this action of epinephrine is not due to facilitation of neuromuscular transmission (83).

Clinical application of dibenamine and other blocking agents is discussed by Yonkman (84), and dibenamine is compared with other agents (ergot alkaloids, benzodioxanes, priscol, and yohimbine) by Nickerson (85).

Related compounds have been studied (86, 87, 88). One of the most potent congeners of dibenamine is α-naphthylmethylethyl-β-bromoethylamine (88). Its actions are essentially similar to those of dibenamine, but it is about twenty times as potent. It "reverses" not only epinephrine but also cobefrine, ephedrine, phenylephrine, amphetamine, and "Privine," but usually not propadrine, paredrine, and paredrinol. "Pitressin" and "Isuprel" are unaffected (89).

Norepinephrine is said not to be reversed by adrenolytic agents, but a fall in pressure can be induced by suitably large doses of norepinephrine after the administration of a large dose of dibenamine (70), confirming the report of von Euler (90, 91) that norepinephrine (arterenol) has inhibitory actions like those of epinephrine, but weaker in degree. The levo isomer, recently described, also has inhibitory actions, though it is said not to be "reversed" by

933 F (92). Bacq (93), von Euler (91), and West (94) believe that norepinephrine must play a physiological role as sympathin E and may be a precursor of epinephrine. Marrazzi (95) objects that norepinephrine cannot be considered to be sympathin E since it has an inhibitory action on ganglionic transmission, but this assumes a rigid definition of sympathin E as a purely excitatory, rather than chiefly excitatory, mediator.

Dihydrogenation of ergot alkaloids increases their adrenolytic activity, decreases toxicity, and decreases direct motor actions on smooth muscle, including the uterus [Rothlin (96)]. Dihydroergotamine (DHE-45) has been studied more extensively than the other alkaloids; toxicity in experimental animals is low: rabbits survive DHE in doses eight times the LD_{50} of ergotamine; it has no significant uterine action and depresses, but usually does not reverse, the pressor action of epinephrine [Orth & Ritchie (97)]. DHE, in contrast to ergotamine, has little or no direct action on blood pressure or blood flow in the dog (98). Although the therapeutic effectiveness of ergot alkaloids in migraine is commonly believed to be related either to vasoconstrictor properties or to a sympatholytic action with attendant changes in intracranial circulation, DHE causes no significant changes in arterial pressure, cerebral blood flow, or oxygen uptake in normal human subjects (99). The possibility remains that changes might occur during migraine attacks.

Dihydroergocornine (DHO-180) more effectively blocks motor actions of epinephrine, is also relatively nontoxic (100), and has had preliminary clinical trial in hypertension and peripheral vascular disease (101, 102).

Both DHE and DHO will prevent ventricular tachycardia induced by epinephrine in animals exposed to chloroform (103) or cyclopropane (100). Although cardiac sympatholytic action is not striking, the action is presumably on the heart, for both compounds are effective in doses which fail to prevent a pressor action of epinephrine [DHE, 0.4 mg. per kg. in the dog (97)]. Unlike other adrenolytic agents, including dibenamine, the dihydrogenated ergot alkaloids have been shown to antagonize inhibitory (rabbit ileum), as well as excitatory, actions of epinephrine (96).

The Fourneau adrenolytic compound, 933 F, has been used as a test for pheochromocytoma. The drug fails to produce a consistent depressor action in normotensive or essential hypertensive

individuals, but does so in cases of pheochromocytoma or during infusion of epinephrine (104). Tetraethylammonium has also been tried in one patient, in whom it induced, like histamine and methacholine (105), a pressor response (106).

Central Interruption of Sympathetic Reflexes

In addition to agents blocking sympathetic mechanisms at ganglia and at the effector cell, evidence has appeared that sympathetic vascular reflexes may be rather specifically abolished by certain 8-aminoquinolines related to pamaquine. Pamaquine, chronically administered to dogs in near-lethal doses, causes paralysis of ocular sympathetic mechanisms, without impairment of ganglionic or peripheral transmission. Blood pressure and heart rate are low, and pressor responses to carotid occlusion or central vagal stimulation are depressed or abolished. Since respiratory reflex mechanisms, as well as reflex vagal bradycardia, persist, the afferent mechanisms appear to be intact, and the lesion must be central [Moe & Seevers (107)]. Pentaquine produces similar actions in the dog and the monkey (108, 109). Alving and co-workers studied the human toxicity of pentaquine extensively in volunteers and observed the development of postural hypotension lasting for weeks after administration of the drug was discontinued (110). Pentaquine has been given to patients with essential hypertension, in whom it induced a reduction of arterial pressure and postural hypotension lasting for days or weeks. Toxic side effects preclude any therapeutic use (111). It is possible that related compounds, capable of producing damage or destruction of specific nuclei in the hypothalamus and brain stem, may become very useful as laboratory tools.

SYNTHETIC ANALGESICS

In the past year a considerable amount of information has accumulated on the synthetic analgesic, methadon; more has been added to our knowledge of merperidine; and a large number of new analgesics have been synthesized.

Analgesic Activity

Methadon and merperidine.—Methadon, since it contains an asymmetric C-atom, occurs in two optically active forms as well as in racemic mixture. Most of the earlier work on this analgesic

was carried out with the latter. The DL-form has been compared with morphine and is stated to be anywhere from 1.3 to 4 times as potent (112 to 116). Most of the analgesic action resides in the L-isomer (113, 115, 117, 118, 119), which is about 70 per cent more potent in rats than racemic methadon (119) and seven times as active as the D-isomer (118). This difference in activity between the D- and L-form apparently increases with the size of the animal. For example, the L-isomer is twenty-five times as active in dogs and fifty times as active in man as the D-isomer (118). In man DL-methadon is approximately ten times as potent as merperidine (116). The duration and intensity of action of DL-methadon and merperidine, like morphine, are increased by neostigmine (112). On the other hand, atropine or scopolamine decreases both the intensity and duration of action of morphine and merperidine, but only the duration of action of DL-methadon.

Methadon has been employed clinically in a variety of conditions with which pain is associated (120 to 126). Oral and parenteral routes have been used with doses ranging from 2.5 to 20 mg. With the lowest doses and the oral route adequate pain relief occurs in only about 10 per cent of the patients. Fair to excellent analgesia occurs in 70 to 100 per cent of cases when larger doses are given parenterally.

Further clinical studies on the analgesic effectiveness of merperidine have been reported. It has been demonstrated to be useful as a preanesthetic medicant, for the postoperative control of pain (125), and of value in conjunction with scopolamine for obstetric analgesia (127).

Pfeiffer *et al.* (128) have pointed out the existence of three different types of pain in man: (a) superficial pain or "Supaine"—bright, fast, epicritic in nature, (b) "Deepain"—dull, aching, protopathic pain, and (c) "Sympain"—pain with a sympathetic component. Dilaudid and heroin have a certain amount of selectivity in the types of pain they allay, whereas L-methadon is characterized by a broad spectrum, obtunding all three types of pain equally.

Other compounds.—A number of derivatives of methadon have been prepared and studied for analgesic activity. 6-Dimethylamino-4, 4-diphenyl-5-methyl-3-hexanone, a structural isomer of methadon (studied by various workers under the name isoamidone), has received considerable experimental attention and a limited clinical trial. It is about one half as potent as methadon in the rat (117,

118) and has about the same therapeutic index. Other workers have reported a higher therapeutic index (129). Similar to methadon, the L-isomer of this compound is most potent analgesically, the DL-form less so and the D-isomer least potent (117). In the normal human DL-isomethadon has the same or greater analgesic potency than DL-methadon (113, 115). The L-isomer has been employed clinically (130, 131) with a high incidence of pain relief and has been stated to be three times as potent as morphine.

Chen (118) has pointed out the effect of various changes in the methadon nucleus on analgesic potency. If the amino nitrogen is removed there is complete loss of activity. The keto and amino groups must be on opposite sides of the diphenyl carbon atom or there is no analgesic action and substitution of one or both phenyl groups decreases or abolishes activity. Variants, with the nitrogen atom in ring or chain form, have a lower activity. Compounds of the type $R \cdot C(C_6H_5)_2 \cdot CH_2 \cdot CH(CH_3) \cdot N(CH_3)_2$ are most promising. Where R is $—CH(OOC \cdot CH_3) \cdot C_2H_5$ the resulting derivative is 30 per cent more active than methadon. The L- and D-isomers of ethyl-4-dimethylamino-2,2-diphenylvalerate have been tested for analgesic activity in the rat and found to be less potent than the corresponding isomers of methadon. In both the methadon and isomethadon series the order of decreasing analgesic potency and increasing analgesic index is ketone, ketimine, acetylketimine (132). 6-Dimethylamino-3,3-diphenyl-2-hexanone has been synthesized and tested for activity in man (133). It is weakly analgesic and produces frequent side actions.

A number of carbinols derived from methadon and isomethadon by reduction of the ketonic oxygen show low analgesic activity (134). Esters of these compounds are relatively potent. Shortening or lengthening of the carbon chain in the methadon series of compounds results in decreased activity (135). Radical alteraations in the basic side chain of methadon results in decreased analgesic potency.

Blicke & Krapcho (136) have prepared a number of ketopiperidines, cyclic analogues of methadon. Only one of the series, a 4-phenyl-4-cyclohexyl derivative, exhibits any analgesic activity. Many piperidine derivatives and partial structures of morphine have been synthesized (137, 138) and have been tested for analgesic activity (139, 140). Lee (140) has made some rather interesting observations on the relationship between the chemical structure

of these compounds and their analgesic activity. Two of the piperidine derivaties have been evaluated in man. 1-Methyl-4-(*m*-hydroxyphenyl)- 4-propionylpiperidine (keto-bemidone) produces excellent analgesia with minimal side actions (133). The *cis* and *trans* forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine have been compared with morphine in man (141). The *cis* form is less potent than morphine but has few side actions while the *trans* form is about equally as active as morphine and has marked and frequent side actions.

Small (142) has recently reviewed the chemistry and synthesis of the newer synthetic analgesics, and Eddy (143) has discussed the newer morphine derivatives and reported on the results obtained thus far in the oral use of metopon for the control of pain in terminal malignancy. The majority of compounds in a series of benzoxazolone derivatives show mild analgesic activity (144). Fellows & Ullyot (145) have reported on the analgesic potency and toxicity in cats of ninety-two aralkylamines. β-Diethylaminoethanol, a hydrolysis product of procaine, has been employed intravenously in man (125) with resultant analgesic effects surpassing those of intravenous procaine.

Other Actions on the Central Nervous System

In the lower dose range (2.5 to 30 mg.) in man, DL-methadon has little or no sedative effect (125, 146) but with higher doses (30 to 75 mg.) sedation and narcosis occur (147, 148). DL-Methadon produces sedation in cold-blooded as well as warm-blooded animals (118), but the amount required for sedation is substantially greater than that for analgesia. The respiratory center is depressed in rabbits (115), dogs (149), and man (113, 115, 121, 147, 148), especially with higher doses. The order of decreasing respiratory depressant potency in the methadon series is: L-methadon, DL-methadon, isomethadon, D-methadon (115). Euphoria is occasionally seen in normal patients (116, 122) and more frequently in former morphine addicts (148). DL-Methadon stimulates the vomiting center in man (114, 116, 124) but not in pigeons, dogs, or monkeys (118). Stimulation of the vagal center in dogs (118) and miosis in man (114) occurs following administration of the drug. Alterations in the electroencephalogram occur in cats (150) without any change in electrospinogram. Like morphine it produces erection of the tail in mice (118) and Leimdorfer (151) explains this action

as a facilitation by increased activity along the cerebrospinal pathways of a normal reflex originating in the cord. Doses of 30 mg. of DL-methadon produce no change in the electroencephalogram in man (114). Chronic decorticate dogs, chronic spinal dogs, and chronic decorticate cats respond to this drug in all respects as they do to morphine (152).

Cardiovascular Actions

In the unanesthetized dog methadon produces bradycardia (152) which, in the anesthetized animal, has been demonstrated to be of central origin (118). Intravenous injection of DL-methadon in the dog under barbital anesthesia produces a marked, acute fall in blood pressure succeeded by a prolonged period of hypotension (153). After a second injection the animal is tolerant to the prolonged but not the acute hypotensive action. L-Methadon produces a fall in blood pressure with the initial injection; subsequent ones give moderate rises after a fleeting fall (117). D-Methadon produces only hypotensive effects. Intravenous merperidine, like DL-methadon, produces a prolonged hypotensive response in the dog with partial to complete tolerance developing on repeated administration (153).

Small oral doses of DL-methadon have no effect on blood pressure, heart rate, or peripheral circulation in man (124). Larger doses consistently produce a bradycardia (113, 147) of sinus origin (147, 148) and a fall in systolic blood pressure (114, 147, 148). Five milligrams intramuscularly in man produce no change in cerebral blood flow (154). The occurrence of circulatory collapse following parenteral methadon and merperidine has been reported (131).

Gastrointestinal and Genitourinary Actions

Isolated rabbit (155) or guinea pig (156) intestine is relaxed by methadon. In the intact unanesthetized animal (118, 149, 157, 158) and man (147) the opposite effect, spasmogenesis and constipation, is observed. Merperidine is less constipating in rats and rabbits than methadon (157). Inactive, isolated uteri always exhibit contractions in the presence of methadon (118). Isolated uteri of rats (155) or hamsters (118), which are always rhythmically active, respond by relaxation. The isolated rabbit uterus may be active or inactive and its response to methadon is always opposite to its own state of motility. Drug induced uterine spasm is relaxed by methadon. In-

dications are that methadon will also relax the ureter (159). Such a spasmolytic action on the ureter and biliary tract was previously claimed for merperidine. Lapides (160) has been unable to demonstrate any action of merperidine on the ureter in the unanesthetized human subject. Gaensler *et al.* (161) have measured the changes in intrabiliary pressure postoperatively in ten patients who had T-tube drainage of the common bile duct. Merperidine was shown to produce spasm of the sphincter of Oddi and marked increases in intrabiliary pressure.

Miscellaneous Studies

In the dog DL-methadon is equally as potent as morphine in producing hyperglycemia (162). Tolerance to this action is developed on continued administration (163). Five milligrams per kilogram of DL-methadon intravenously in rabbits produce the same quantitative hyperglycemic response as 10 mg. per kg. of morphine (118). Phatak *et al.* (164) have investigated the hyperglycemic response of rabbits to morphine, L-methadon, DL-methadon, DL-isomethadon, and merperidine as a possible method for estimating addiction potentialities. All compounds produce a hyperglycemia and during development of tolerance the greatest response is to L- and DL-methadon. On withdrawal the greatest response is in those animals which have received L-methadon. In former human addicts single doses of DL-methadon have no effect on the blood sugar level (114, 148) and during repeated administration of the drug in these individuals the blood sugars remain in the low normal range (147).

DL-Methadon and merperidine have local anesthetic properties (rabbit's cornea, intracutaneous wheal in man) (165) but are very irritating. DL-Methadon also has a weak antihistaminic action (118). Single injections of DL-methadon produce hypothermia in the dog (152) and man (114, 148). In the dog merperidine has been shown to decrease the amount of cyclopropane, ether, or thiopental required to produce a given plane of anesthesia (125). Cronheim & Ware (166) have devised a method for the estimation of methadon and presented data showing that only a small amount of administered drug is excreted unchanged in the urine.

A number of papers have appeared relative to the effects of methadon and merperidine on enzymes and intermediary metabolism. The oxidation of glucose, pyruvate, and lactate by rat brain

cortex slices is inhibited by methadon and merperidine as is anerobic glycolysis of cerebral homogenates [Elliott *et al.* (167)]. These workers have postulated inhibition of oxidation by these two analgesics at the dehydrogenase level rather than at the flavoprotein level. Grieg (168) has confirmed Elliott's results on inhibition of glycolysis by methadon and her findings suggest that this action is primarily due to inhibition of hexokinase. Rat diaphragm behaves like rat brain in that low concentrations of methadon stimulate oxygen uptake whereas high concentrations inhibit it (169). Only inhibition of oxygen uptake occurs when methadon is added to surviving rat liver or kidney slices. Merperidine has been shown to depress oxygen consumption of human placenta (170) and methadon to have the same qualitative effects it has on rat brain cortex slices. Brain cholinesterase is inhibited by methadon (171). Abreu *et al.* (154) have been unable to demonstrate any significant effect of 5 mg. of methadon injected intramuscularly on the oxygen consumption of cerebrum in the normal human subject.

Toxicity

Jenney & Pfeiffer (172), Hoppe & Miller (173), Finnegan *et al.* (163), Haag *et al.* (162), and Chen (118) have determined the acute, subacute, and chronic toxicity of the methadons, isomethadons, and certain other derivatives in various animal species and compared them with morphine. In general, methadon and most of its closely related derivatives are more toxic than morphine in all species studied. Henderson & Chen (174) have found that methadon, unlike morphine, shows no increased toxicity in weanling or aged rats. A number of untoward toxic effects of methadon and isomethadon have been noted in man but these seem to be rather infrequent, especially in the nonambulatory patient (120). The most frequently reported side effects are nausea, dizziness, vomiting, respiratory depression, and diaphoresis (112, 113, 116, 121 to 124, 126, 130, 131, 146). Mental confusion and toxic psychoses may develop in elderly patients on prolonged use of methadon (120, 125).

Tolerance, Habituation, and Addiction

Tolerance to one or more of the following actions of methadon in the rat, dog, and chronic decorticate dog has been demonstrated: analgesia, hyperglycemia, sedation, miosis, respiratory depression,

hypothermia, and circulatory actions (149, 158, 163, 175, 176, 177). It is not possible to determine in the lower species whether or not psychic dependence occurs (178). Isbell *et al.* (175), Wikler & Frank (176), and Wikler (177) claim that physical dependence to methadon and abstinence on withdrawal occur in the dog. Scott *et al.* (158) were unable to observe any withdrawal symptoms in the dog following chronic administration of methadon. Little or no tolerance to the respiratory depressant and sedative-narcotic actions of methadon develops in the monkey (178) and there are minimal signs of abstinence on withdrawal of the drug.

In man (former morphine addicts) tolerance develops to the analgesic, emetic, sedative-narcotic, and miotic actions of DL-methadon and DL-isomethadon (179). Euphoria results from the use of these compounds but not from D-methadon or methadol. In morphine addicts DL-methadon will completely substitute for morphine (175, 180, 181) and when withheld there results a relatively mild abstinence syndrome. L-Methadon also substitutes adequately. DL-Isomethadon is only partially effective (181), a morphine like abstinence syndrome resulting on withdrawal. D-Methadon and methadol are ineffective substitutes for morphine in addicts. In individuals without previous addiction experience methadon does not appear to produce any degree of physical dependence or abstinence symptoms on withdrawal following prolonged administration (116, 121, 122, 123, 124). Recent evidence also indicates that in such individuals long continued use of meperidine may result in psychic dependence with little or no physical dependence (182, 183).

LITERATURE CITED

1. HUNT, R., *J. Pharmacol. Exptl. Therap.*, **28**, 367–88 (1926)
2. ING, H. R., *Physiol. Revs.*, **16**, 527–44 (1936)
3. BURN, J. H., AND DALE, H. H., *J. Pharmacol. Exptl. Therap.*, **6**, 417–38 (1915)
4. ACHESON, G. H., AND MOE, G. K., *J. Pharmacol. Exptl. Therap.*, **84**, 189–95 (1945)
5. ACHESON, G. H., AND MOE, G. K., *J. Pharmacol. Exptl. Therap.*, **87**, 220–36 (1946)
6. ACHESON, G. H., AND PEREIRA, S. A., *J. Pharmacol. Exptl. Therap.*, **87**, 273–80 (1946)
7. ACHESON, G. H., AND PEREIRA, S. A., *Federation Proc.*, **5**, 161 (1946)
8. MOE, G. K. (Unpublished data)
9. HOLMES, P. E. B., JENDEN, D. J., AND TAYLOR, D. B., *Proc. Intern. Physiol. Congr., 17th Congr., Oxford*, 191–92 (1947)

10. Birchall, R., Taylor, R. D., Lowenstein, V. E., and Page, I. H., *Am. J. Med. Sci.*, **213**, 572–78 (1947)
11. Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R., *Am. J. Med. Sci.*, **213**, 315–23 (1947)
12. Gruhzit, O. M., Fisken, R. A., and Cooper, B. J., *J. Pharmacol. Exptl. Therap.*, **92**, 103–7 (1948)
13. Keston, A. S., and Wortis, S. B., *Proc. Soc. Exptl. Biol. Med.*, **61**, 439–40 (1946)
14. Brown, G. E., Wood, E. H., and Lambert, E. H., *J. Pharmacol. Exptl. Therap.*, **93**, 10–17 (1948)
15. Lyons, R. H., Hoobler, S. W., Neligh, R. B., Moe, G. K., and Peet, M. M., *J. Am. Med. Assoc.*, **136**, 608–13 (1948)
16. Levinson, J. E., Reiser, M. F., and Ferris, E. B., *J. Clin. Invest.*, **27**, 154–55 (1948)
17. Hayward, G. W., *Lancet*, **I**, 18–20 (1948)
18. Moss, W. G., and Wakerlin, G. E., *Federation Proc.*, **7**, 82–83 (1948)
19. Malton, S. D., Hoobler, S. W., Ballantine, H. T., Lyons, R. H., Neligh, R. B., Cohen, S. L., and Moe, G. K., *Univ. Hosp. Bull., Ann Arbor*, **14**, 5–8 (1948)
20. Hoobler, S. W., Malton, S. D., Ballantine, H. T., Neligh, R. B., and Lyons, R. H. (Unpublished data)
21. Green, H. D., and Ogle, B. C., *Federation Proc.*, **7**, 43 (1948)
22. Larsson, Y., and Frisk, A. R., *Acta Med. Scand.*, Suppl. No. 196, 212–21 (1947)
23. Boyd, A. M., Crawshaw, G. R., Ratcliffe, A. H., and Jepson, R. P., *Lancet*, **I**, 15–18 (1948)
24. Ray, T., Burch, G. E., and de Bakey, M. E., *New Orleans Med. Surg. J.*, **100**, 6–16 (1947)
25. Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, G. K., and Sutler, M. R., *Surgery*, **20**, 525–35 (1946)
26. Coller, F. A., Campbell, K. N., Berry, R. L., Sutler, M. R., Lyons, R. H., and Moe, G. K., *Ann. Surg.*, **125**, 729–55 (1947)
27. Ballantine, H. T., Hoobler, S. W., Malton, S. D., and Lyons, R. H. (Unpublished data)
28. Reiser, M. F., and Ferris, E. B., *J. Clin. Invest.*, **27**, 156–63 (1948)
29. Taylor, R. D., Underwood, L. C., and Page, I. H., *J. Lab. Clin. Med.*, **32**, 1491–95 (1947)
30. Hoobler, S. W., Moe, G. K., Rennick, B. R., Neligh, R. B., and Lyons, R. H., *Univ. Hosp. Bull., Ann Arbor*, **13**, 9–10 (1947)
31. Holt, J. F., Lyons, R. H., Neligh, R. B., Moe, G. K., and Hodges, F. J., *Radiology*, **49**, 603–10 (1947)
32. Chapman, W. P., Stanbury, J. B., and Jones, C. M., *J. Clin. Invest.*, **27**, 34–38 (1948)
33. Neligh, R. B., Lyons, R. H., Holt, J. F., Hoobler, S. W., and Moe, G. K., *Gastroenterology* (In press)
34. Farah, A. (Personal communication, 1947)

35. Whitrock, R. M., Tieche, H. L., and Seevers, M. H., *Federation Proc.*, **7**, 265 (1948)
36. Oppenheimer, M. J. (Personal communication, 1946)
37. Whitrock, R. M., and Moe, G. K. (Unpublished data)
38. Collins, D. A., *Federation Proc.*, **7**, 21–22 (1948)
39. Zweig, M., Steigmann, F., and Meyer, K. A., *Federation Proc.*, **7**, 268 (1948)
40. Little, J. M., Ogle, B. C., Yeagley, J. D., and Cayer, D., *Science*, **106**, 448–49 (1947)
41. Nesbit, R. M., Lapides, J., Valk, W. W., Sutler, M. R., Berry, R. L., Lyons, R. H., Campbell, K. N., and Moe, G. K., *J. Urol.*, **57**, 242–50 (1947)
42. Root, M. A., *Federation Proc.*, **6**, 366 (1947)
43. Lapides, J., *J. Urol.*, **59**, 501–33 (1948)
44. Moe, G. K., Rennick, B. R., Hoobler, S. W., Neligh, R. B., and Lyons, R. H., *J. Lab. Clin. Med.*, **32**, 311 (1947)
45. Page, I. H., and Taylor, R. D., *Science*, **105**, 622 (1947)
46. Corcoran, A. C., and Page, I. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 148–51 (1947)
47. Page, I. H., Taylor, R. D., and Reinhard, J. J., *Federation Proc.*, **7**, 89–90 (1948)
48. Page, I. H., and Taylor, R. D., *J. Am. Med. Assoc.*, **135**, 348–49 (1947)
49. Moe, G. K., *J. Am. Med. Assoc.*, **137**, 1115–16 (1948)
50. Freyburger, W. A., Capo, L. R., and Moe, G. K., *Federation Proc.*, **7**, 220 (1948)
51. Bülbring, E., Burn, J. H., and de Elío, F. J., *J. Physiol. (London)*, **107**, 222–32 (1948)
52. Moe, G. K., *Proc. Intern. Physiol. Congr., 17th Congr., Oxford*, 327 (1947)
53. Boelaert, R. E., *Arch. intern. pharmacodynamie*, **75**, 417–18 (1948)
54. Moe, G. K., Capo, L. R., and Peralta, B., *Am. J. Physiol.*, **153**, 601–5 (1948)
55. Capo, L. R., and Moe, G. K. (Unpublished data)
56. Morrison, J. L., *Federation Proc.*, **6**, 359–60 (1947)
57. Reardon, M. J., Marzoni, F. A., and Hendrix, J. P., *Federation Proc.*, **6**, 364 (1947)
58. Rennick, B. R., Moe, G. K., Lyons, R. H., Hoobler, S. W., and Neligh, R. B., *J. Pharmacol. Exptl. Therap.*, **91**, 210–17 (1947)
59. Acheson, G. H. (Personal communication, 1947)
60. Freyburger, W. A., and Moe, G. K. (Unpublished data)
61. Chou, T. C., and de Elio, F. J., *Brit. J. Pharmacol.*, **2**, 268–70 (1947)
62. Marrazzi, A. S., and Marrazzi, R. N.. *J. Neurophysiol.*, **10**, 167–78 (1947)
63. Bülbring, E., *J. Physiol. (London)*, **103**, 55–67 (1944)
64. Stanbury, J. B., *J. Pharmacol. Exptl. Therap.*, **93**, 52–62 (1948)
65. Koppanyi, T., and Vivino, A. E., *Federation Proc.*, **5**, 186–87 (1946)
66. Van Harreveld, A., and Feigen, G. A., *J. Neurophysiol.*, **11**, 141–48 (1948)
67. Schallek, W., and Wiersma, C. A. G., *J. Cellular Comp. Physiol.*, **31**, 35–47 (1948)

68. NICKERSON, M., AND GOODMAN, L. S., *J. Pharmacol. Exptl. Therap.*, **89**, 167–85 (1947)
69. NICKERSON, M., AND NOMAGUCHI, G. M., *J. Pharmacol. Exptl. Therap.*, **93**, 40–51 (1948)
70. MOE, G. K., CAPO, L. R., AND FREYBURGER, W. A. (Unpublished data)
71. BIÖRCK, G., *Acta Physiol. Scand.*, **14**, 174–85 (1947)
72. DE VLEESCHHOUWER, G. R., *Proc. Soc. Exptl. Biol. Med.*, **66**, 151–52 (1947)
73. SIMEONE, F. A., AND SARNOFF, S. J., *Surgery*, **22**, 391–401 (1947)
74. HAIMOVICI, H., *Proc. Soc. Exptl. Biol. Med.*, **64**, 486–88 (1947)
75. WILBURNE, M., KATZ, L. N., RODBARD, S., AND SURTSHIN, A., *J. Pharmacol. Exptl. Therap.*, **90**, 215–23 (1947)
76. HAIMOVICI, H., AND MEDINETS, H. E., *Proc. Soc. Exptl. Biol. Med.*, **67**, 163–66 (1948)
77. ACHESON, G. H., FARAH, A., AND FRENCH, G. N., *Federation Proc.*, **6**, 305 (1947)
78. YOUMANS, W. B., AND RANKIN, V. M., *Proc. Soc. Exptl. Biol. Med.*, **66**, 241–44 (1947)
79. NICKERSON, M., AND NOMAGUCHI, G. M., *Federation Proc.*, **7**, 247 (1948)
80. MOE, G. K., MALTON, S. D., FREYBURGER, W. A., AND RENNICK, B. R., *J. Lab. Clin. Med.*, **32**, 1415 (1947)
81. OGDEN, E., *Federation Proc.*, **7**, 87 (1948)
82. NICKERSON, M. (Personal communication, 1948)
83. MADDOCK, W. D., RANKIN, V. M., AND YOUMANS, W. B., *Proc. Soc. Exptl. Biol. Med.*, **67**, 151–53 (1948)
84. YONKMAN, F., *Natl. Med. Chem. Symposium, Am. Chem. Soc., 1st Meeting* 81–86 (1948)
85. NICKERSON, M., *Natl. Med. Chem. Symposium, Am. Chem. Soc., 1st Meeting*, 70–80 (1948)
86. LOEW, E. R., MICETICH, A., AND ACHENBACH, P., *Federation Proc.*, **6**, 351–52 (1947)
87. HUNT, C. C., *Federation Proc.*, **7**, 229 (1948)
88. DE VLEESCHHOUWER, G. R., *Proc. Soc. Exptl. Biol. Med.*, **67**, 298–99 (1948)
89. WELLS, J. A., AND RALL, D. P., *Federation Proc.*, **7**, 264 (1948)
90. EULER, U. S. v., *Acta Physiol. Scand.*, **12**, 73–97 (1946)
91. EULER, U. S. v., *Proc. Intern. Physiol. Congr., 17th Congr., Oxford*, 70–72 (1947)
92. TAINTER, M. L., TULLAR, B. F., AND LUDUENA, F. P., *Science*, **107**, 39–40 (1948)
93. BACQ, Z. M., AND FISCHER, P., *Arch. intern. physiol.*, **55**, 73–91 (1947)
94. WEST, G. B., *J. Physiol. (London)*, **106**, 426–30 (1947)
95. MARRAZZI, A. S., AND MARRAZZI, R. N., *Science*, **106**, 520–21 (1947)
96. ROTHLIN, E., *Bull. acad. Suisse sci. Medicales*, **2** (4) (1946–47)
97. ORTH, O. S., AND RITCHIE, G., *J. Pharmacol. Exptl. Therap.*, **90**, 166–73 (1947)
98. KARR, N. W., *Federation Proc.*, **7**, 232 (1948)
99. ABREU, B. E., LIDDLE, G. W., BURKS, A. L., SIMON, A., SUTHERLAND, V., AND GORDAN, G. S., *Federation Proc.*, **7**, 201 (1948)

100. Orth, O. S., Capps, R. A., and Suckle, H. M., *Federation Proc.*, **6**, 361 (1947)
101. Bluntschli, H. J., *S. African Med. J.*, **21**, 21–23 (1947)
102. Bluntschli, H. J., and Goetz, R. H., *S. African Med. J.*, **21**, 382–401 (1947)
103. Liebenow, R. R., and Orth, O. S., *Federation Proc.*, **6**, 350 (1947)
104. Goldenberg, M., Snyder, C. H., and Aranow, H., *J. Am. Med. Assoc.*, **135**, 971–76 (1947)
105. Guarneri, V., and Evans, J. A., *Am. J. Med.*, **4**, 806–13 (1948)
106. La Due, J. S., Murison, P. J., and Pack, G. T., *Proc. Am. Federation Clin. Research*, **3**, 67–68 (1947)
107. Moe, G. K., and Seevers, M. H., *Federation Proc.*, **5**, 193–94 (1946)
108. Moe, G. K., Peralta, B., and Seevers, M. H. (Unpublished data)
109. Richardson, A. P., Walker, H. A., and Miller, B. S., *Proc. Soc. Exptl. Biol. Med.*, **65**, 258–61 (1947)
110. Craige, B., Eichelberger, L., Jones, R., Alving, A. S., Pullman, T. N., and Whorton, C. M., *J. Clin. Invest.*, **27**, 17–24 (1948)
111. Freis, E. D., and Wilkins, R. W., *Proc. Soc. Exptl. Biol. Med.*, **64**, 455–58 (1947)
112. Christensen, E. M., and Gross, E. G., *J. Am. Med. Assoc.*, **137**, 594–99 (1948)
113. Denton, J. E., Straus, O. H., Waddell, W. E., and Beecher, H. K., *Federation Proc.*, **7**, 214–15 (1948)
114. Isbell, H., Wikler, A., Eisenman, A. J., and Frank, K., *Federation Proc.* **6**, 341 (1947)
115. Thorp, R. H., Walton, E., and Ofner, P., *Nature*, **160**, 605–6 (1947)
116. Troxil, E. B., *J. Am. Med. Assoc.*, **136**, 920–23 (1948)
117. Luduena, F. P., Miller, L. C., Ananenko, E., and Frick, J. D., *Federation Proc.*, **7**, 241–42 (1948)
118. Chen, K. K., *Ann. N. Y. Acad. Sci.* (In press)
119. Miller, L. C., *Ann. N. Y. Acad. Sci.* (In press)
120. Batterman, R. C., and Oshlag, A. M., *Federation Proc.*, **7**, 206 (1948)
121. Bercel, N. A., *Diseases Nervous System*, **9**, 15–18 (1948)
122. Kirchhof, A. C., and David, N. A., *Federation Proc.*, **6**, 345 (1947)
123. Kirchhof, A. C., and David, N. A., *Anesthesia & Analgesia*, **27**, 92–100 (1948)
124. Popkin, R. J., *Am. Heart J.*, **35**, 793–99 (1948)
125. Rovenstine, E. A., *Ann. N. Y. Acad. Sci.* (In press)
126. Ishmael, W. K., and Stacy, J. R., *J. Oklahoma State Med. Assoc.*, **40**, 454–56, 468 (1947)
127. Hershenson, B. B., *Ann. N. Y. Acad. Sci.* (In press)
128. Pfeiffer, C. C., Sonnenschein, R. R., Glassman, L., Jenney, E. H., and Bogolub, S., *Ann. N. Y. Acad. Sci.* (In press)
129. Sherrod, T. R., Kaiser, R., Santos-Martinez, J., and Pfeiffer, C. C., *Federation Proc.*, **7**, 255 (1948)
130. Gentling, A. A., and Lundy, J. S., *Proc. Staff Meetings Mayo Clinic*, **22**, 249–51 (1947)
131. Bieter, R. N., and Hirsh, S. A., *Ann. N. Y. Acad. Sci.* (In press)

132. CHENEY, L. C., SMITH, R. R., AND BINKLEY, S. B., *Abstracts Am. Chem. Soc. 113th Meeting*, 2K (Chicago, April, 1948)
133. KIRCHHOF, A. C., *Federation Proc.*, **7**, 234 (1948)
134. SPECTER, M. E., BYRD, W. M., AND CHENEY, L. C., *Abstracts Am. Chem. Soc., 113th Meeting*, 1K–2K (Chicago, April, 1948)
135. THORP, R. H., WALTON, E., AND OFNER, P., *Nature*, **159**, 679–80 (1947)
136. BLICKE, F. F., AND KRAPCHO, J., *Abstracts Am. Chem. Soc., 113th Meeting*, 3K–4K (Chicago, April, 1948)
137. ZIERING, A., BERGER, L., HEINEMAN, S. D., AND LEE, J., *J. Org. Chem.*, **12**, 894–903 (1947)
138. ZIERING, A., AND LEE, J., *J. Org. Chem.*, **12**, 911–14 (1947)
139. FOSTER, R. H. K., AND CARMAN, A. J., *J. Pharmacol. Exptl. Therap.*, **91**, 195–209 (1947)
140. LEE, J., *Natl. Med. Chem. Symposium, Am. Chem. Soc., 1st Meeting*, 227–28 (1948)
141. HOLLAND, H. L., AND GROSS, E. G., *Federation Proc.*, **7**, 227–28 (1948)
142. SMALL, L., *Ann. N. Y. Acad. Sci.* (In press)
143. EDDY, N. B., *Ann. N. Y. Acad. Sci.* (In press)
144. CLOSE, W. J., TIFFANY, B. D., AND SPIELMAN, M. A., *Abstracts Am. Chem. Soc., 113th Meeting*, 2K–3K (Chicago, April, 1948)
145. FELLOWS, E. J., AND ULLYOT, G. E., *Natl. Med. Chem. Symposium, Am. Chem. Soc., 1st Meeting*, 35–49 (1948)
146. KIRCHHOF, A. C., AND DAVID, N. A., *Western J. Surg. Obstet. Gynecol.*, **55**, 183–86 (1947)
147. ISBELL, H., EISENMAN, A. J., WIKLER, A., DAINGERFIELD, M., AND FRANK, K., *Federation Proc.*, **6**, 264 (1947)
148. ISBELL, H., EISENMAN, A. J., WIKLER, A., AND FRANK, K., *J. Pharmacol. Exptl. Therap.*, **92**, 83–89 (1948)
149. SCOTT, C. C., CHEN, K. K., KOHLSTAEDT, K. G., ROBBINS, E. B., AND ISRAEL, F. W., *J. Pharmacol. Exptl. Therap.*, **91**, 147–56 (1947)
150. LEIMDORFER, A., *Arch. intern. pharmacodynamie*, **76**, 153–62 (1948)
151. LEIMDORFER, A., *Federation Proc.*, **7**, 239 (1948)
152. WIKLER, A., FRANK, K., AND EISENMAN, A. J., *Federation Proc.*, **6**, 384 (1947)
153. SHIDEMAN, F. E., AND JOHNSON, H. T., *J. Pharmacol. Exptl. Therap.*, **92**, 414–20 (1948)
154. ABREU, B. E., LIDDLE, G. W., BURKS, A. L., SIMON, A., SUTHERLAND, V., AND GORDON, G. S., *Federation Proc.*, **7**, 201 (1948)
155. UCHIYAMA, J., KIRCHHOF, A. C., AND DAVID, N. A., *Proc. Soc. Exptl. Biol. Med.*, **66**, 417–18 (1947)
156. KIRCHHOF, A. C., AND UCHIYAMA, J. K., *Federation Proc.*, **6**, 345–46 (1947)
157. KARR, N. W., *Federation Proc.*, **6**, 343 (1947)
158. SCOTT, C. C., KOHLSTAEDT, K. G., ROBBINS, E. B., AND ISRAEL, F. W., *Federation Proc.*, **6**, 370 (1947)
159. LEE, H. M. (Unpublished data)
160. LAPIDES, J., *J. Urol.*, **59**, 501–33 (1948)
161. GAENSLER, E. A., MCGOWAN, J. M., AND HENDERSON, F. F., *Surgery*, **23**, 211–20 (1948)

162. HAAG, H. B., FINNEGAN, J. K., AND LARSON, P. S., *Federation Proc.*, **6**, 234 (1947)
163. FINNEGAN, J. K., HAAG, H. B., LARSON, P. S., AND DREYFUSS, M. L., *J. Pharmacol. Exptl. Therap.*, **92**, 269–76 (1948)
164. PHATAK, N. M., MALONEY, J., AND DAVID, N., *Federation Proc.*, **7**, 249 (1948)
165. EVERETT, G., *Anesthesiology*, **9**, 115–20 (1948)
166. CRONHEIM, G., AND WARE, P. A., *J. Pharmacol. Exptl. Therap.*, **92**, 98–102 (1948)
167. ELLIOTT, H. W., WARRENS, A. E., AND JAMES, H. P., *J. Pharmacol. Exptl. Therap.*, **91**, 98–102 (1947)
168. GRIEG, M. E., *Arch. Biochem.*, **17**, 129–37 (1948)
169. BACHELOR, A. L., AND ELLIOTT, H. W., *Federation Proc.*, **7**, 203–4 (1948)
170. JAMES, H. P., AND PAGE, E. W., *Federation Proc.*, **7**, 230 (1948)
171. EADIE, G. S., BERNHEIM, F., AND FITZGERALD, D. B.. *Federation Proc.*, **7**, 216 (1948)
172. JENNEY, E. H., AND PFEIFFER, C. C., *Federation Proc.*, **7**, 231 (1948)
173. HOPPE, J. O., AND MILLER, L. C., *Federation Proc.*, **7**, 228 (1948)
174. HENDERSON, F. G., AND CHEN, K. K., *Proc. Soc. Exptl. Biol. Med.* (In press)
175. ISBELL, H., WIKLER, A., EDDY, N. B., WILSON, J. L., AND MORAN, C. F., *J. Am. Med. Assoc.*, **135**, 888–94 (1947)
176. WIKLER, A., AND FRANK, K., *Federation Proc.*, **6**, 384 (1947)
177. WIKLER, A., *Federation Proc.*, **7**, 265 (1948)
178. SEEVERS, M. H., *Ann. N. Y. Acad. Sci.* (In press)
179. ISBELL, H., *Ann. N. Y. Acad. Sci.* (In press)
180. ISBELL, H., EISENMAN, A. J., WIKLER, A., DAINGERFIELD, M., AND FRANK, K., *Federation Proc.*, **6**, 340–41 (1947)
181. ISBELL, H., AND EISENMAN, A. J., *Federation Proc.*, **7**, 162 (1948)
182. CURRY, J. J., *J. Am. Med. Assoc.*, **133**, 243–44 (1947)
183. BATTERMAN, R. C., *Ann. N. Y. Acad. Sci.* (In press)

AUTHOR INDEX

A

Abarbanel, A. R., 24
Abbott, B. C., 298, 301, 307, 320, 326
Abbott, H. L., 73
Abbott, J. A., 218
Abbott, W. E., 512
Abdon, N. O., 417
Abelin, I., 56, 61
Abels, J. C., 66
Ablondi, F., 448
Abolins, L., 33
Abrahm, P. M., 505
Abrams, A., 357
Abrams, M., 451
Abramson, D. I., 445
Abreu, B. E., 572, 577, 579
Achenbach, P., 571
Acheson, G. H., 416, 565, 568, 569, 570
Ackerman, E. M., 420
Ackermann, W. W., 8
Adams, A. E., 6
Adams, E., 370, 377, 379
Adams, J. M., 370, 374, 376
Adams, W. L., 111
Adams, W. S., 534
Addis, T., 494, 497, 510
Ades, H. W., 237, 238, 260
Adler, H. F., 474, 484
Adlersberg, D., 454
Adolf, M. S., *see* Spiegel-Adolf, M.
Adolph, E. F., 104, 289
Adolph, W., 396, 441
Adrian, E. D., 166, 204, 217, 269
Ågren, G., 117, 341
Aguirre, F., 391
Ahlborg, N. G., 509
Ahlenstiel, H., 259
Ahlstrom, L., 358
Ahrens, E. H., Jr., 91
Ajo, A., 247
Albanese, A. A., 85
Albaum, H. G., 413
Albe-Fessard, D., 179
Albright, F., 67, 68
Albrink, W. S., 440, 517
Alella, A., 478, 479
Aleshin, B. V., 56
Alexander, B., 124
Alexander, R. S., 92, 153, 440, 458
Alford, T. C., Jr., 130
Alford, W. C., 85
Allardyce, J., 59
Allen, C. R., 152, 447
Allen, W. F., 239
Alles, G. A., 194
Allison, J. B., 437
Allsopp, C. B., 528
Almquist, J. O., 33
Almy, T. P., 113
Alpern, M., 251
Alpers, B. J., 327
Alstad, G., 90
Alstead, S., 126
Althausen, T. L., 83, 509
Altman, K. I., 335
Altmann, F., 235
Altschul, R., 327
Altschule, M. D., 391, 416, 446
Altyale, A. M., 397
Alveryd, A., 480
Alving, A. S., 452, 494, 573
Ambache, N., 119, 150
Amberson, W. R., 312, 514 518
Ambrose, A. M., 458
Ames, S. R., 413
Amoroso, E. C., 23
Amoroso, M. D., 200, 216
Ampil, D., 144
Amprino, R., 15, 16
Ananenko, E., 574, 575, 577
Andelman, M. B., 215
Andereggen, P., 482
Anderson, A., 115
Anderson, D., 67
Anderson, E., 534
Anderson, R., 327
Anderson, R. C., 457
Anderson, R. S., 312
Anderson, W. L., 111
Andreasen, E., 66, 358, 359, 365, 372
Andrew, N. V., 362
Andrew, W., 362
Anfinsen, C. B., 11
Angerer, C. A., 415
Angier, R. B., 341
Anker, H. S., 72
Anlyan, A. J., 72, 360
Annegers, J. H., 107, 123, 126
Anslow, W. P., Jr., 509
Anson, B. J., 388
Anson, M. L., 321
Anthony, D. S., 537
Anthony, E., 533
Apter, J. T., 278
Aramburu, T., 337, 339, 340
Arana, R., 69, 149
Aranow, H., 344, 573
Archibald, R. M., 439, 495, 500, 501, 512, 516
Arieff, A. J., 327
Armstrong, B. E., 338
Armstrong, S. H., Jr., 91
Arnason, T. J., 536
Arocha, H. G., 374
Aron, H., 369
Artom, C., 123, 511
Arzac, J. P., 24, 26, 51
Aschaffenburg, R., 29
Aschkenasy, A., 56
Asdell, S. A., 36
Ashburn, L. L., 344
Ashby, M. C., 216, 222
Ashby, W. R., 205
Ashenbrucker, H., 337, 345
Ashman, J. S., 509
Ashman, R., 410
Ashworth, C. T., 85, 86, 389, 510
Astbury, W. T., 311, 312, 313, 315, 317, 319, 321, 322, 323
Åström, K. E., 189, 190
Astwood, E. B., 59, 60, 61
Atkinson, W. B., 24
Aub, J. C., 37, 440
Aubert, X., 304, 307
Auerbach, O., 407
Aumann, K. W., 148
Aurin, M. C., 556
Auscher, C., 69
Austin, G. M., 252
Avery, A., 89
Axelrod, A. E., 378
Axelrod, A. R., 345, 368
Ayer, J. L., 507
Aykin, S., 556

B

Babkin, B. P., 110, 111
Bach, L. M. N., 168, 483
Bachelor, A. L., 579
Bachrach, W. H., 111
Baclesse, F., 535

Bacon, J. S. D., 13
Bacq, Z. M., 139, 141, 146, 195, 484, 572
Badenoch, A. W., 453
Badenoch, W. W., 512
Baez, S., 90, 438, 449
Bagchi, B. K., 200, 217
Bageant, W. E., 152, 472
Baggenstoss, A. H., 117
Bahnson, E. R. 83
Bailey, C. C., 50
Bailey, K., 311, 312, 313, 314, 316, 317, 322, 323
Bailey, P., 162, 163
Bain, G. P., 470
Bain, W. A., 147
Baisset, A., 221
Baker, B. L., 65
Baker, R. F., 561
Baker, S. L., 515
Bakey, M. E. de, *see* de Bakey, M. E.
Bakker, A., 245
Bakos, A. C. P., 399, 472
Baldes, E. J., 442
Baldock, G. R., 201
Baldwin, E., 73
Baldwin, F. M., 442
Baldwin, J., 400, 471
Bale, W. F., 121
Balfour, D. C., 114
Balfour, W. M., 84
Ball, S., 250
Ballantine, H. T., 567
Ballich, N. L., 476, 481
Ballin, H. M., 207, 212
Baltz, J. I., 83
Bandes, J., 110
Banerjee, D., 339
Banerjee, R. P., 124
Banerjee, S., 63
Banfield, W. G., 401
Banga, I., 311
Banks, H. W., Jr., 5
Bannon, R. E., 249
Barach, A. L., 470, 471, 475, 484
Barach, B., 475
Bárány, E., 246, 247, 248, 260, 555, 559
Barbour, I., 201
Barclay, A. E., 451, 496
Barclay, J. A., 69, 452, 456, 497, 506
Barcroft, H., 307, 445
Barcroft, J., 479
Bard, P., 162
Barenne, J. G. D. de, *see* Dusser de Barenne, J. G.
Barer, R., 299, 301, 311, 312, 319
Barfred, A., 60
Barger, A. C., 477, 484
Barker, H. G., 494
Barker, P. S., 410
Barker, S. B., 52, 53, 60
Barker, S. H., 161, 207, 260
Barlow, H. B., 252
Barnard, R. D., 252, 341
Barnard, W. G., 91
Barnes, J. M., 64
Barnes, K. K., 528, 534, 535
Barnes, R. H., 128
Barnes, T. C., 185, 199, 200, 213, 215, 216, 553
Barnett, H. L., 499, 505
Baronofsky, I. D., 115, 127, 128
Barrett, A. M., 360
Barrett, E., 494, 497
Barrett, H. W., 56
Barrillou, S. L., *see* Lamotte-Barrillou, S.
Barrington, E. J. W., 116
Barron, D. A., 189
Barron, D. H., 16, 478
Barron, E. S. G., 2, 346, 360, 528, 534, 536
Barroso-Moguel, R., 389
Barry, A., 391
Bartels, E. C., 59, 60
Barth, L. G., 9
Bartlett, G. R., 360
Bartlett, S., 29
Bartley, S. H., 259
Barton, H. C., 85
Barton, M. N., 362
Barton, R. W., 85
Bassett, D. L., 23
Bassett, R. C., 200, 217
Bastman-Heiskanen, L., 104
Bastos, A. T., *see* Tavares Bastos, A.
Basu, M. N., 472
Basu, N. M., 122
Basu, U. P., 124
Batchelder, A. C., 552
Bates, P. L., 125
Bate-Smith, E. C., 306, 325
Batten, W., 503
Batterman, R. C., 574, 579, 580
Baudouin, A., 199, 217, 218
Bauer, F. C., Jr., 390
Baumann, C. A., 57
Baumberger, J. P., 477, 484
Baumgardt, E. L. M., 253, 254
Baxter, J. H., 87, 510
Baxter, J. H., Jr., 146
Baxter, J. S., 363, 370
Baylies, H., 23
Bazell, A. H., 88
Beach, F. A., 38
Beams, A. J., 85
Bean, J. W., 473
Bean, W. B., 90
Bear, R. S., 298, 311, 312, 319
Beattie, J., 84
Beck, E., 162
Becker, R. F., 291
Beckman, E. L., 447
Beebe, H., 242
Beecher, H. K., 574, 575, 576, 577, 579
Beevers, C. A., 216, 222
Behrmann, V. G., 477, 484
Bein, H. J., 247
Békésy, G. von, *see* von Békésy, G.
Belding, H., 338
Belding, H. W., 104
Belford, J., 84, 86, 420, 421
Belgovskaya, A. A. P., *see* Prokofyeva-Belgovskaya, A. A.
Bell, D. J., 13
Bell, P. G., 247
Bellac, F. J., 505
Bellotti, M., 120
Belt, M., 341
Bénard, H., 86
Benda, C. E., 68
Benda, P., 470
Benda, R., 470
Bendall, J. R., 306, 325
Bender, M. B., 255, 260
Bender, S., 27
Bendheim, O. L., 200
Benhamou, E., 374
Benjamin, B., 341
Benjamin, J. A., 33
Bennett, L. L., 68, 70, 71
Benoit, J., 73
Bensley, C. M., 24
Bercel, N. A., 221, 574, 576, 579, 580
Beresford, E. N., 221
Berger, E. Y., 505

Berger, L., 575
Berger, R., 51
Bergman, H. C., 91, 405, 407, 448, 471
Berk, J. E., 83
Berkson, J., 61
Berliner, R. W., 506
Berman, D., 66
Berman. J. K., 125
Berman, L., 345, 368
Berman, M., 309, 417, 418
Berner, F. W., 484
Bernhard, C. G., 189, 190, 191
Bernhard, K., 126
Bernheim, F., 579
Berry, M. R., 442
Berry, R. G., 327
Berry, R. L., 458, 566, 567
Berthrong, M., 88, 89
Bertrand, I., 202, 208
Beshore, D. L. G., 478
Besman, L., 124
Bessey, O. A., 360
Best, C. H., 86, 87
Betheil, J. L., 59
Bethell, F. H., 338, 341
Betz, H., 327
Beutner, R., 185, 553
Beyer, K. H., 508
Bialliart, J. P., 247
Bianco, P. D., 35
Bicknell, F., 62
Biddulph, C., 38, 52
Bielig, H. J., 338
Biering-Sørensen, K., 93
Bierman, W., 110, 327
Biesele, J. J., 359, 366
Bieter, R. N., 575, 577, 579
Bieth, R., 6
Bigelow, J., 205, 278
Bindra, D., 287, 288
Binet, L., 151, 154, 470, 478, 480, 483
Bing, H. I., 307
Bing, J., 66, 360, 378, 508
Bing, R. J., 398, 400, 406, 448, 471
Binkley, F., 323, 325
Binkley, S. B., 575
Biörck, G., 407, 570
Birath, G., 476, 484
Birchall, R., 452, 458, 566
Bird, O. D., 340
Bird, R. M., 346
Bird, S., 30
Birge, R., 387, 389
Birnberg, C. H., 2, 32
Biro, I., 249
Bischler, A., 560
Bischler, V., 560
Bischoff, F., 30, 555, 557
Bishop, F. W., 531, 535
Bishop, G. H., 310
Bishop, L. F., 407
Bissell, A., 55
Bissett, N. G., 27
Bitterman, M. E., 259
Bixby, E. M., 68
Bjergaard, K. P., *see* Pedersen-Bjergaard, K.
Bjerner, B., 216
Bjørneboe, M., 378
Bjurstedt, H., 308
Black, D. A. K., 123
Black, R., 26, 90
Black, R. H., 517
Black, S. P. W., 164, 165
Blair, H. A., 125, 179, 421
Blakemore, A. H., 91
Blalock, A., 91
Blanchet, E., 24, 26, 51
Bland, E. F., 142
Blandau, R. J., 26
Blank, I. H., 561
Blicke, F. F., 575
Blier, J. S., 221
Blinkov, S. M., 217
Blinn, K. A., 476, 484
Bliss, A. F., 250
Bloch, E. H., 91, 459
Bloch, I., 552
Bloch, K., 48, 72
Block, K., 335
Block, M., 111
Block, M. H., 533
Block, S., 114
Block, W. D., 495
Blokhin, N. N., 536
Blondheim, S. H., 410
Blood, D. W., 451
Bloom, F., 509
Bloom, M. A., 537
Bloom, W., 377, 532, 537
Bloom, W. L., 358
Bloomfield, R. A., 400, 402
Blumenthal, L. S., 454
Bluntschli, H. J., 458, 572
Boas, E. P., 454
Bobb, J. R. R., 406, 439
Bocchiotti, S., 117, 120
Boccuzzi, G., 115
Boche, R. D., 475, 531
Bock, H., 308
Bodansky, O., 327, 419
Bodenstein, D., 8
Bodnar, S. R., 415, 457
Boelaert, R. B., 484
Boelaert, R. E., 568
Boeri, E., 475, 477, 478, 484
Boettner, F. E., 511
Bogolub, S., 574
Bohn, C. L. S., 341
Bolletti, A., 121
Bollman, J. L., 86, 89, 91, 114, 123
Bolton, C., 91
Bonduelle, A., 471
Bondy, P. K., 65, 87
Bone, A. H., 63
Bonham, K., 530, 531
Bonin, G. von, *see* von Bonin, G.
Bonnar, W. McK., 445
Bonnerdel, R., 327
Bonnet, V., 180, 184, 189
Bonnycastle, D. D., 435
Bonsnes, R. W., 494
Bonvallet, M., 179, 483
Booker, W. M., 446
Boone, B. R., 390
Boos, M. H., *see* Hodel-Boos, M.
Boothe, J. H., 341
Borchardt, P. R., 410
Bordley, J. E., 242
Borell, U., 61
Borglin, N. E., 417
Borison, H. L., 144, 145, 482
Borkowski, W. J., 207, 214, 327
Bornstein, M. B., 213
Boroughs, E. D., 121
Bosma, F., 252
Bosma, J. F., 163, 208
Boss, W. R., 14
Boström, C. G., 258
Botelho, S., 477, 484
Bottin, J., 117
Bouckaert, J. J., 451
Boulet, L., 150
Boulet, M. A., 150
Bouman, M. A., 254, 255
Bound, J. P., 123
Bounes, G. C., 216
Bourguignon, G., 308, 327
Bourliére, F., 327
Boutwell, J. H., 126
Bovet, D., 484
Bowden, R. E. M., 327
Bowles, L. L., 245
Boy, G., 327

Boyarski, L. L., 184
Boyarsky, L. H., 23, 327
Boyd, A. M., 567
Boyd, E. M., 94
Boyd, L. J., 113, 445
Boyd, T. E., 399
Boyd, W. E., 202
Boyle, M. N., 458
Boyle, P. J., 324
Bozler, E., 119, 308, 408
Boynton, R. E., 448
Bracci, U., 121
Brachet, J., 3, 9
Bradbury, J. T., 34
Bradford, N. M., 108
Bradley, G. P., 92, 442, 446, 496, 504
Bradley, S. E., 92, 442, 446, 453, 496, 504
Brady, T. G., 558
Brambell, F. W. R., 11, 12, 36
Brand, J., 46
Brandenburg, R. O., 340
Brandt, M. B., 67
Brannon, E. S., 146, 398, 400, 401, 402, 472
Brannon, S., 397
Branson, H., 5
Brauer, R. W., 356, 360
Brauner, L., 553
Braun-Vallon, S., 257
Braverman, I., 314, 317
Bray, C. W., 235
Brazier, M. A. B., 212, 213, 327
Brecht, K., 473
Breckenridge, C. G., 70
Breckler, I. A., 59
Breed, E. S., 400
Bremer, F., 161, 186, 189, 199, 204, 205, 297
Brendler, S. J., 483
Brieger, H., 86
Briggs, R., 4
Brihaye, J., 192
Brinegar, W. C., 222
Brink, F., 176, 194
Brisac, C., 200, 216, 218, 222
Britton, S. W., 447
Brobeck, J. R., 154
Brock, M. J., 360
Brock, W. A. van den, *see* van den Brock, W. A.
Brockmyre, F., 346
Brodie, O. J., 421
Brody, B., 218, 219
Brody, D. A., 106, 107
Brody, S., 58, 480
Broemser, P., 458
Broh-Kahn, R. H., 46, 114
Broido, A., 527
Bromberg, Y. M., 28
Bromiley, R. B., 273, 274
Bronk, D. W., 145, 162, 176, 193, 194
Brontman, M., 401
Brookhart, I. M., 399
Brooks, A. A., 200
Brooks, C. McC., 154, 189, 192, 194
Brooks, M. M., 1, 547
Brooks, S. C., 547
Brooks, V. B., 185
Brooksbank, B. W. L., 27
Brosene, W. G., Jr., 448
Brouwer, S. W., 83
Brown, A., 344, 552
Brown, D. E. D., *see* Denny-Brown, D. E.
Brown, D. F., 527
Brown, E., 445, 448
Brown, E. A., 469
Brown, E. B., 478, 484
Brown, E. F., 58
Brown, F., 472
Brown, G. E., 566
Brown, G. L., 195, 304, 305
Brown, H. M., 125
Brown, H. R., 415
Brown, H. S., 111
Brown, P., 35
Brown, R. A., 340
Brown, R. H., 253
Brown, W. M. C., 533
Browne, J. S. L., 68
Brownell, K. A., 65
Brozek, J., 249, 259
Broyer, T. C., 552
Brucer, M., 459, 470
Bruckner, I., 372, 374
Brues, A. M., 531, 536
Brumberg, E. M., 254
Brunaud, M., 118
Bruner, H. D., 471, 475
Brunkow, M. D., 127
Brunschwig, A., 86
Brust, M., 306
Bruzzone, S., 34
Bryan, F. A., 532
Bryant, J. M., 410
Brzezinski, A., 28
Buchanan, O. H., 495
Bucher, G. R., 114, 115
Bucher, K., 481, 482, 484
Buchthal, F., 217, 297, 298, 300, 306, 317, 323, 324
Buchwald, K. W., 51
Buck, R. C., 454
Bucy, P. C., 162
Buettner, R. J., 532
Buffington, M. A., 201
Bugnard, L., 201, 221
Bühlmann, A., 478
Bülbring, E., 70, 148, 149, 195, 304, 456, 568, 569
Bull, A. L., 6
Bull, H. B., 108, 299, 302, 306, 320, 321, 323
Bullet, F., 126
Bullock, T. H., 194, 195, 213, 309
Bunde, C. A., 35, 414
Bunn, D., 83
Bunn, E., 398
Bunoan, P. B., 406
Bunting, H., 49, 50, 440, 517
Burch, G. E., 401, 567
Burchell, H. B., 400
Burgen, A. S. V., 50
Burges, H. C., 410
Burian, H. M., 255, 257
Burkhardt, J., 36
Burkhoder, T. M., 505
Burks, A. L., 572, 577, 579
Burmester, B. R., 368
Burn, J. H., 29, 70, 148, 149, 456, 565, 568
Burns, B. D., 195, 304
Burrows, W., 124
Burstein, M., 151, 154, 470, 472, 473, 478
Burton, A. C., 495
Burwell, C. S., 473
Busch, E., 217
Bushard, W. J., 249
Bussard, A., 35
Busse, E. W., 478
Bustad, L. K., 30
Butcher, E. O., 23
Butt, H. R., 83
Butturini, U., 415
Byer, J., 443
Byers, S. O., 505
Byrd, W. M., 575

C

Cabrera Cosio, E., 393, 409, 410
Cacioppo, F., 115
Cahill, W. M., 362

Cain, J., 222
Cain, J. C., 91
Cairns, H., 234
Caldwell, M. J., 13
Callaghan, J. P., 493
Callan, H. G., 4
Callander, J., 130
Callen, I. R., 346
Callender, S., 121
Callender, S. T. E., 344
Calvery, H. O., 560
Cambar, R., 484
Cameron, A. T., 361, 365
Cameron, D. G., 85, 346
Cameron, G. R., 355, 367, 473
Campbell, D., 257
Campbell, G. S., 469, 478, 484
Campbell, J., 88
Campbell, J. A., 83
Campbell, J. G., 72
Campbell, K. N., 458, 566, 567
Campbell, P. N., 122
Campbell, R. J., 270
Campori, A. S., 112
Canadell, J. M., 57
Canepa, J. F., 87, 117
Cannon, P. R., 374, 377
Cannon, W. B., 148
Cantarow, A., 30, 31, 94
Cantor, M. M., 50
Cantril, S. T., 527
Canzanelli, A., 71
Capo, L. R., 568, 570, 571
Capps, R. A., 572
Capsey, P. A., 50
Caputto, R., 47
Carey, E. J., 327
Cargill, W. H., 400, 472
Carhart, R., 241
Carl, G. P., 456
Carlotti, J., 390
Carlson, F. D., 176
Carlson, L. D., 484
Carman, A. J., 575
Carmichael, H. T., 162
Carmichael, J., 361, 365
Carmichael, L., 259
Carothers, E. L., 120
Carpenter, C. P., 86, 505
Carrea, R. M. E., 165, 166 167
Carryer, H. M., 478
Cartaya, J. A., 121
Carter, A. C., 38
Carter, B. B., 378
Cartwright, G. E., 336, 337, 338, 340, 344, 345, 348
Caruso, A., 470
Carvallo, J. R., *see* Rivero Carvallo, J.
Casady, R. B., 36
Casals, J., 85
Casarett, G. W., 335
Cascio, G., 115
Case, T. J., 214
Casella, C., 484
Casey, E. J., 141
Casida, L. E., 23
Cassels, D. E., 436
Castellanos, A., 390
Castellanos, H., 359
Castillo, H., 390
Castillo, J. C., 470
Cate, J. T., *see* Ten Cate, J.
Cathcart, R. T., 458
Cattell, M., 307
Cavelti, E. S., 511
Cavelti, P. A., 511
Cavett, J. W., 55
Cayer, D., 567
Ceballos Labat, J., 390
Celis, A., 390
Cerecedo, L. R., 30
Cervino, J. M., 37
Chacko, L., 252
Chadwick, L. E., 184, 442, 443, 473, 474
Chaikoff, I. L., 53, 54, 55, 56, 87, 123
Chakrabarty, M. L., 62
Chamberlain, W. E., 390
Chambers, R., 438, 560
Chambers, W. W., 166
Champeau, M., 56
Champy, C., 406
Chandler, B. F., 245
Chang, A., 348
Chang, H. T., 163
Chang, M. C., 3, 31
Chanutin, A., 67, 367, 374
Chapanis, A., 249, 253
Chapin, J. L., 479
Chapman, E. M., 538
Chapman, W. P., 119, 567
Chappell, R. H., 21, 389
Chapple, E. D., 212
Chapple, W. A. C., 85
Chardon, G., 148, 153, 370
Charipper, H. A., 68, 343
Charlier, R., 484
Charlwood, P. A., 12, 30
Chase, J. H., 363, 374, 375, 376
Chase, S. W., 459
Chase, W. E., 374, 377
Chasis, H., 453, 499, 505, 509
Chatfield, P. O., 482
Chatonnet, J., 482
Chauchard, B., 145
Chauchard, P., 145
Chaudhury, S. G., 552
Chavez, I., 390
Chen, G., 411, 458
Chen, K. K., 457, 574, 575, 576, 577, 578, 579, 580
Cheney, L. C., 575
Cheney, R. H., 2
Chenoweth, M. B., 409
Chernoff, H. M., 408
Chernov, V. M., 115
Cherry, R., 448
Chesnut, J. L., 396
Cheymol, J., 327, 418, 477, 484
Chilcote, M. E., 72
Chin, H., 219
Chinn, B., 312
Chittum, J. R., 448
Chodnik, K. S., 115, 120
Chou, T. C., 569
Christensen, B. G., 342
Christensen, E. L., *see* Landboe-Christensen, E.
Christensen, E. M., 574, 579
Christensen, N. O., 378
Christensen, W. R., 444
Christman, A. A., 495
Chudzek, E. B., 56
Chuinard, E. G., 327
Chung, H. L., 348
Chuprakov, A., 255, 256
Chusid, J. G., 163, 164, 208
Ciaramelli, L. C., 68, 370, 374
Cier, J. F., 153, 482
Cisneros, F., 396, 441
Cizek, L. J., 509
Claesson, L., 21, 22, 34
Clagett, O. T., 117
Clark, B., 256
Clark, B. B., 109, 111
Clark, D. E., 87
Clark, G., 25, 482
Clark, J. K., 494
Clark, J. R., 339
Clark, K. B., 247
Clark, S. L., 217

Clark, W. E. L., 252, 327
Clark, W. F., 517
Clark, W. M., 335
Clarke, D., 90
Clarke, I. G., 458
Clarke, R. W., 453, 497
Claude, A., 413
Clavert, J., 73, 365
Cleghorn, R. A., 439
Clement, G., 149
Clemmesen, J., 347
Clemmeson, V., 256
Cleveland, H. C., 388
Cline, J. K., 341
Cloche, R., 218
Close, J. R., 302
Close, W. J., 576
Clouse, C., 444
Cobb, D. M., 174
Cobb, S., 199, 252
Cobb, W. A., 199, 202, 204, 216
Code, G. F., 112
Cogan, D. G., 248, 559
Cogswell, H. D., 125
Cohen, E. J., 38
Cohen, J. A., 49, 360
Cohen, L., 533
Cohen, M. E., 390
Cohen, P. P., 83, 357
Cohen, S. L., 567
Cohn, C., 92
Cohn, E. J., 345
Cohn, R., 200, 204, 216, 221, 222, 252, 389
Cohn, W. E., 527
Colcher, A., 93
Colcher, H., 83, 91, 502
Cole, F., 127
Cole, H. H., 23, 36
Cole, K. S., 561
Cole, W. H., 437, 439
Colldahl, H., 478
Coller, F. A., 567
Collier, J. G., 10
Collings, W. D., 449, 495
Collins, D. A., 119, 567
Collins, F. D., 250
Collins, V. J., 444
Collo, F. D., *see* Dal Collo, F.
Colowick, S. P., 45, 46
Comanduras, P. D., 83
Comanesco, V., 92
Comfort, M. W., 117, 126, 338
Comroe, J. H., 477, 484
Comroe, J. H., Jr., 327, 396, 401
Comsa, J., 359
Conan, N. J., 442
Condiff, H., 493
Conklin, R. E., 152
Conn, J. W., 68
Connelly, C. M., 176
Connon, F. E., 10
Connors, W. M., 2
Conrad, M., 200
Console, A. D., 141
Conway, E. J., 324, 555, 557, 558
Cook, C. D., 85
Cooke, D. S., 68
Cooke, P. M., 162, 165
Cooke, R. C., 121
Cooke, W. T., 69, 123, 452, 456, 497
Coon, G. P., 156
Cooney, E. A., 91
Cooper, B. J., 458, 566
Cooper, F. W., Jr., 458
Cooper, R. S., 13
Copazzi, L., 250
Cope, O., 355, 363
Copenhaver, W. M., 7, 388
Coppée, G., 195
Corcoran, A. C., 440, 453, 458, 494, 505, 513, 518, 568
Corday, E., 407
Cordier, D., 476, 477, 479, 484
Cordier, G., 476, 477, 479, 484
Cordiez, E., 32
Corey, E. L., 483
Cori, C. F., 45, 46, 47, 48
Cori, G. T., 46
Corkill, A. B., 47, 48
Cornil, L., 222
Corrado, M., 248, 252
Correll, J. W., 454
Cortezziani, E., 418
Cortrell, R., 154
Corvazier, R., 12
Cosio, E. C., *see* Cabrera Cosio, E.
Coss, J. A., Jr., 528
Cossio, P., 389
Cottet, P., 390
Couch, J. R., 5
Coujard, R., 37
Coulson, R. A., 493
Cournand, A., 397, 400, 401, 402, 410, 471, 472, 474
Courrier, R., 30
Courtice, F. C., 355, 367, 473
Covolo, G. C., 51
Cowgill, G. R., 30
Cowie, A. T., 51, 65
Cowie, D. B., 27, 28, 246, 555, 560
Cox, L. W., 59
Cox, W. M., Jr., 85
Coyer, D., 128
Crabtree, W. B., 118
Craddock, C. G., 534
Craddock, C. G., Jr., 370, 373, 534
Crafts, R. C., 343, 344
Craig, F. N., 480
Craige, B., 573
Cramer, F., 217
Crandall, L. A., Jr., 92
Crandall, W. C., 443
Crane, E. E., 109, 558
Cravens, W. W., 5, 340
Craver, B. N., 535, 536
Craver, L. E., 538
Craver, L. F., 368, 531
Crawford, B. H., 253
Crawshaw, G. R., 567
Cremerius, J., 222
Crescitelli, F., 184, 214
Crisp, D. J., 484, 550, 551, 552
Cristini, G., 246
Critchfield, F. H., 505
Crittenden, P., 417
Cromartie, W. J., 358
Cronheim, G., 578
Crosby, E. C., 164, 248
Crosby, R. C., 91
Crosley, A. P., 453
Crosley, A. P., Jr., 497
Crouch, C. L., 260
Crowe, S. J., 236
Cruickshank, E. W. H., 435
Cruz, W. O., 344
Culbertson, J. T., 260
Culbertson, J. W., 442
Cullinan, J. F., 327
Culotta, C. S., 53
Culver, B., 337
Cumming, E., 536
Cummins, G. M., 127
Cunha, T. J., 30
Cunningham, L., 64
Cure, C., 221
Currens, J. H., 449
Curry, J. J., 92, 580
Curtis, G. M., 53
Curtiss, L. F., 527

Cushing, V. D., 94
Cuthbertson, E. M., 510
Cutting, M., 498
Cytronberg, S. S., 115

D

Daft, F. S., 340, 344
Dahlstrom, H., 479
Daingerfield, M., 576, 577, 578, 580
Dainty, M., 315, 323
Dal Collo, F., 478
Dale, H. H., 565
Dalgard, J. B., 89
Daly, I. de B., *see* de Burgh Daly, I.
Damas, H., 15
Dameron, J. T., 127
Dameshek, W., 338, 339, 348
Damodaran, K., 84
Damodaran, M., 344
Dandy, W. E., 235
D'Angelo, S. A., 68
Daniel, L. J., 341
Daniel, P., 496
Daniel, P. M., 451
Danielopolu, D., 372, 374
Danowski, T. S., 59, 60, 400, 506, 510, 555, 556, 557
Darby, W. G., 260
Darby, W. J., 338, 339, 341
Dardinski, V. J., 514
D'Ardois, G. S., *see* Somolinos D'Ardois, G.
Darling, D. B., 344
Darmady, E. M., 512
Darrow, C. W., 201, 203, 205, 218
Darrow, D. C., 370
Davenport, H. W., 108, 109
Davenport, V. D., 91
David, N. A., 574, 576, 577, 578, 579, 580
David, P. L., 416
Davidoff, L. M., 167
Davidson, C. S., 84
Davidson, L. S. P., 338, 339
Davies, R. E., 108, 109, 558
Dávila, M., 122
Davis, G. D., 162
Davis, H., 232, 235, 242, 327
Davis, J. E., 341
Davis, L., 162
Davis, L. J., 344
Davis, M. E., 6, 27
Davis, P. L., 124
Davis, P. W., 221
Davis, R. E., 126
Davis, R. M., 362
Davis, S. N., 253
Davis, W. D., 416, 449
Davison, C., 167
Davson, H., 246, 247, 555, 559
Davtyan, O. K., 551
Dawes, G. S., 406
Dawson, G. D., 203, 210, 220
Dawson, H., 122
Day, P. L., 336
Dayrit, C., 457
Dean, R. B., 551
Dean, R. F. A., 8
Deane, H. W., 67, 69, 89, 362
Dearborn, W. F., 259
Deasy, C. L., 552
de Bakey, M. E., 567
de Barenne, J. G. D., *see* Dusser de Barenne, J. G.
De Beer, E. J., 470
De Beer, G. R., 15, 16
de Burgh Daly, I., 152, 473
De Busscher, G., 471
Decherd, G. M., Jr., 441
DeCoursey, E., 532
DeEds, F., 458
de Elío, F. J., 70, 148, 394, 456, 568, 569
Defosse, G., 360
de Grailly, R., 469
Deichmann, W., 494
Deitrick, J. E., 71
De la Barreda, P., 454
De Lachica, A., 115
Delage, B., 557
De Lalla, V., 474
De Langlade, E., 120
Delarue, R., 218
Delaunois, A. L., 484
Delay, J., 199, 219
Del Castillo, A. L. A., 115
DeLeonibus, D., 249
De Lerner, S. J., 374
Delgado, J. M. R., 156, 162, 208, 211, 483
Dell, M., 218
Dell, P., 151, 483
Deller, J. F. P., 249
Delluva, M., 70
de Loof, J., 304
Delor, R. A., 340
Delsaneas, D. J., 413
De Meio, R. H., 30
de Meyer, J., 308
de Molina, A. F., 454
de Muylder, C., 496
Dempsey, E. W., 312, 360, 361
Dempster, W. T., 327
de Muro, P., 129
Denison, A. B., 440
Denny-Brown, D. E., 191
Dennis, E. W., 443, 444, 458
de Nó, R. L., *see* Lorente de Nó, R.
Denolin, H., 395
Denslow, J. S., 327
Denstad, J., 390
Dent, C. E., 83, 93, 122
Denton, J. E., 574, 575, 576, 577, 579
Denton, R. W., 89
Denues, A. R. T., 311
Denz, F. A., 362
Deringer, M. K., 530, 531
Dern, R. F., 302
Dern, R. J., 125
DeRobertis, E., 55
Dertinger, B. L., 456, 457
Derudder, A., 149
DeSalva, S., 143
Desbarats, M. L., 123
Deschangra, J., 390
Desclaux, P., 70, 71
Desdaux, P., 388
Desgrez, H., 178
deTakats, G., 452
De Turk, W. E., 495
Detwiler, S. R., 15, 16, 17, 245
Dety, S. S., 406
Deuel, H. J., Jr., 57, 59, 85
Deutsch, A., 317, 324, 412
Deutsch, H. F., 30
De Venanzi, F., 374
de Vleeschhouwer, G. R., 458, 484, 570, 571
deVries, H., 254, 259
DeVries, S., 247
DeWaele, H., 49
Dexter, L., 448, 449, 453, 473
Deyrup, I. J., 399
Diaz, C. J., 454

Diaz-Guerrero, R., 59, 216, 327, 359
Dick, G. F., 390
Dick, T. S. B., 218
Dickie, A., 367, 533
Dickman, S. R., 528
Dierker, M., 494
Diethelm, O., 222
Dille, R. S., 341
Dimitropoulos, E., 32
Dingle, J. T., 338
DiPalma, J. R., 399, 400, 444
Dirken, M. N. J., 476
Dittebrandt, M., 495
Dixon, J. L., 127
Dmochowski, L., 365
Doan, C. A., 348, 538
Dobeneck, H. v., 335
Dobriner, K., 495
Dobson, H. L., 416
Dobson, R. L., 534, 539
Dock, W., 83, 91, 403, 510
Dodd, K., 406
Dodds, D. C., 83
Dodds, E. C., 515
Dodgson, K. S., 31
Dodson, L. B., 5
Doesschate, G. ten, *see* ten Doesschate, G.
Doesschate, J. ten, *see* ten Doesschate, J.
Dohan, F. C., 61
Doi, Y., 318
Doisy, E. A., 35
Dole, V. P., 439, 500, 501, 508, 512, 516, 550, 553
Dolgin, M., 389, 410
Dolidze, S. V., 304
Dolivo, M., 482
Doljanski, L., 86
Domanski, B., 93
Domart, A., 470
Dominguez, R., 494
Donaldson, E. C., 67
Donaldson, L. R., 530, 531
Donhoffer, S., 103
Doniger, J., 530
Donland, C. P., 528, 538
Donno, L., 470
Dontigny, P., 364, 451, 455
Dorbecker, N., 390
Dorfman, R. I., 38
Döring, G. K., 479
Dougherty, G. W., 120
Dougherty, T. F., 58, 66, 359, 361, 363, 364, 365, 366, 368, 369, 370, 371, 373, 374, 375, 376
Douglas, G. F., Jr., 117
do Valle, J. E., 419
Dovey, V. J., 201, 203, 208, 209, 216, 219
Dow, D. J., 222
Dow, P., 397, 398, 399
Dowdy, A. H., 371, 533
Dowling, C. V., 416
Downing, A. C., 307, 320, 326
Downman, C. B. B., 125, 144
Doxtader, E. K., 458
Drabkin, D. L., 49, 50, 89
Dragstedt, L. R., 87, 129
Draize, J. H., 560
Drake, C. G., 164, 165
Draper, W. B., 478
Dresdale, D., 400, 410, 471, 472
Dreyfus, J. C., 327
Dreyfuss, M. L., 578, 579, 580
Drill, V. A., 20, 84, 86, 88, 90, 91
Drillien, C. M., 36
Drinker, C. K., 355, 356, 473
Dripps, R. D., 401
Driscoll, P. E., 360
Driver, R. L., 401, 406
Droogleever-Fortuyn, J., 161, 167, 205, 211, 220
Druault, A., 247
Druault, S., 247
Drury, D. R., 474, 498
Dryer, R. L., 114, 128
Dubach, R., 344
Dubash, J. J., 345
Dubois-Poulson, A., 249
Dubreuil, P., 27
Dubuisson, M., 298, 302, 313, 323, 324, 325
Duchosal, P. W., 410
Dugal, L. P., 103
Duguet, J., 247
Duke, H., 473
Duke, K. L., 22
Duke-Elder, W. S., 246, 555, 559
Dumont, J., 148
Dumont, M., 51
Dumont, P., 247
Duncan, C. P., 279
Dunn, A. L., 201, 215
Dunn, M. S., 84
Durach, D., 121
Duran-Reynals, F., 38
Durant, T., 410
Dury, A., 368, 371, 557
Dusser de Barenne, J. G., 278
Dustin, P., Jr., 359
Duvall, E. N., 327
Duvigneaud, A. R., *see* Rochon-Duvigneaud, A.
du Vigneaud, V., 495
Dvoskin, S., 53
Dynes, J. B., 216

E

Eadie, G. S., 579
Eagle, H., 503, 505
Eakin, R. M. 23
Earl, J. T., 94
Earle, D. D., Jr., 91
Earle, D. P., Jr., 502, 505
Eaton, A. G., 509
Ebling, F. J., 37
Eccles, J. C., 173, 174, 189, 192, 194, 199, 213, 297, 310
Eckenhoff, J. E., 400, 401, 406, 415, 448
Eckman, M., 475
Eckstein, R. W., 416
Eddy, J. H., Jr., 84
Eddy, N. B., 576, 580
Edholm, O. G., 445
Edman, P., 117, 455
Edwards, C. T., 113
Edwards, L. E., 113
Edwards, P. C., 341
Efimov, V. V., 105
Eggleston, N. M., 495
Ehrich, W. E., 105, 373, 376, 377, 378
Eichelberger, L., 573
Eickhoff, L. F. W., 216, 222
Eidlow, S., 406
Eijk, M. van, *see* van Eijk, M.
Eiler, J. J., 509
Eilert, M. L., 87
Eisen, H. N., 66, 374, 375, 377
Eisenman, A. J., 574, 575, 576, 577, 578, 580
Ekehorn, G., 506
Elam, J. O., 397, 478, 484
Elder, W. S. D., *see* Duke-Elder, W. S.
Eldred, E., 161, 165

Elek, S. R., 396
Elftman, H., 50
Elfo, F. J. de, *see* de Elfo, F. J.
Elion, G. B., 340
Eliot, T. S., 459
Elkinton, J. R., 59, 400, 494, 506
Elkins, E. C., 327
Ellenberg, M., 63
Ellinger, F., 529, 535
Ellinger, G. F., 390
Ellinger, P., 493
Elliott, H. W., 52, 412, 458, 579
Elliott, J. R., 511
Elliott, K. A. C., 554
Ellis, D., 118, 470
Ellis, F., 530
Elmadjian, F., 368, 371
Elman, R., 85
Elvehjem, C. A., 5, 214, 340, 344, 413
Elwell, L. E., 473
Emerson, G. A., 340
Emerson, K., Jr., 439, 500, 501, 512, 516
Emery, D. A., 257
Emery, F. E., 90
Emmelin, M., 119
Emmelin, N., 150
Emmens, C. W., 32, 33, 54
Enachesco, M., 92
Endicott, E. T., 85
Endicott, K. M., 346
Engbaek, L., 182, 324
Engel, F., 65
Engel, F. L., 495
Engel, G. L., 201, 212, 214, 216
Engel, M. G., 495
Engel, R. W., 344
Engelhardt, V. A., 301, 310, 314, 317, 323
Engle, E. T., 24
Engstrom, R. M., 368
Ensor, C. R., 415, 458
Entenman, C., 123
Entenman, E., 56
Eppinger, E. C., 473
Epstein, B. S., 391
Epstein, M., 340
Erdös, T., 306, 312, 325
Erickson, T. C., 214
Eriksen, C. W., 280
Ershoff, B. H., 59
Erway, W. F., 52
Escardo, F., 218
Eschenbrenner, A. B., 530, 531, 532
Escher, D. J. W., 370
Espersen, T., 347
Essex, H. E., 442
Essman, L., 557
Estaban, M., 252
Estren, S., 348
Etienne, L., 57
Euler, C. v., 125, 144, 179, 190
Euler, H. v., 357, 358
Euler, U. S. v., 145, 146, 417, 457, 472, 480, 493, 571, 572
Evans, H. M., 30, 33, 51, 65, 68, 70, 71, 370, 374
Evans, J. A., 573
Evans, J. D., 346
Evans, J. M., 473
Evans, J. N., 247
Evans, L., 87
Evans, R. D., 440
Evans, T. C., 61, 528, 531, 538
Evans, W. A., Jr., 436
Everett, G., 578
Everett, G. M., 215
Everett, J. W., 36, 67, 84
Everett, N. B., 27
Eyring, H., 321
Eyster, J. A. E., 308, 408

F

Faber, M., 390
Faberg, A. C., 529
Fagraeus, A., 360, 377, 378
Fairweather, D. S., 211, 215, 219
Fajer, A. B., 105
Falco, E. A., 340
Falkenhausen, von, *see* von Falkenhausen
Farah, A., 421, 567, 570
Farber, S. J., 505
Farr, L. E., 518, 519
Fasciolo, J. C., 401
Faulkner, R. R., 344
Faure, J., 201, 208
Fauteux, M., 398, 407
Favour, C. B., 368
Fawcett, D. W., 12
Fay, J., 337, 340, 345
Fehily, L., 253
Feigen, G. A., 194, 569
Feil, H. S., 410
Feindel, W. H., 169, 217
Feiner, M., 90
Feinstein, B., 302
Feld, E. A., 184, 555, 559
Feldberg, W., 119, 150, 194, 195
Felder, R. E., 237
Feldman, M., 104, 107, 130, 399
Feldman, R. S., 284
Feller, D. D., 54
Fellows, E. J., 457, 576
Feng, T. P., 180, 184
Fenn, W. O., 174, 321, 323, 325, 401, 442, 443, 473, 474, 475, 478, 484
Fenton, P. F., 30
Ferguson, F. P., 509
Ferguson, J. H., 441
Ferguson, L. K., 145
Ferguson, R. L., 214
Ferin, J., 25, 62
Ferris, B. G., Jr., 444
Ferris, D. O., 119, 120
Ferris, E. B., 212, 214, 216, 566, 567
Fessard, A., 179, 189
Fessard, D. A., *see* Albe-Fessard, D.
Fhipse, R. J., 13
Ficari, A., 129
Fidlar, E., 441
Field, J., 483
Field, J. B., 533
Fields, W. S., 161
Fillenz, M., 195
Filley, G. L., 476, 481
Finch, C. A., 121, 370
Findlay, D., 61, 538
Findley, T., 416, 449
Fine, J., 92, 126, 440, 512
Finerty, J. C., 309, 327
Finesinger, J. E., 212, 561
Fink, A., 441, 459
Fink, E., 335
Fink, K., 534
Finkel, M. P., 537, 538
Finkelstein, M., 90, 419
Finkle, R. D., 537
Finn, M., 127
Finnegan, J. K., 578, 579, 580
Finocchi, G., 483
Finzi, N. S., 538
Fischer, C. C., 216
Fischer, E., 298, 311, 327
Fischer, G., 395
Fischer, H., 324, 335
Fischer, I., 357
Fischer, P., 313, 572

Fischgold, H., 200, 216, 217, 218, 219, 222
Fischlewitz, J., 484
Fischmann, A., 105
Fischmann, E. J., 105
Fischer, I., 72
Fischer, K. C., 556
Fischer, R., 143
Fisher, R. B., 109
Fisher, R. G., 221
Fishman, J. B., 71, 366
Fishman, W. H., 38, 72, 360, 436, 510, 511
Fisken, R. A., 458, 566
Fitch, B., 327
Fitch, H. M., 341
Fitzgerald, D. B., 579
Fizzell, J. A., 327
Flamant, F., 253
Fleisch, A., 482
Fleisch, A. F., 327
Fleischmann, W., 59
Fleischner, F. J., 390
Fleming, A. J., 398
Flexner, J., 514
Flexner, L. B., 27, 28, 555, 560
Flink, E. B., 518
Flinker, M. L., 395
Flock, E. V., 89, 91, 123
Fluharty, R. G., 59
Foà, P. P., 63
Foley, J. M., 484
Folkers, K., 337
Folley, S. J., 29, 30, 51, 65
Folts, L., 144
Foltz, E. L., 401, 406
Fontan, M., 471
Forbes, A. P., 67
Forbes, T. R., 23
Foreman, R. C., 407, 437
Formijue, P., 60
Forsgren, E., 110
Forsham, P. H., 68, 370, 374
Forster, F. M., 207, 214, 327
Forster, R. E., 2nd, 444
Forster, R. P., 450
Fortuyn, J. D., *see* Droogleever-Fortuyn, J.
Foster, R. F., 530
Foster, R. H. K., 575
Foster, R. T., 125
Foster, W. C., 55
Foster, W. L., 444
Fotheringham, W. T., *see* Tejerina-Fotheringham W.
Foulger, J. H., 398
Foulks, J., 506
Fourman, L. P. R., 123
Fournier, J. C. M., *see* Mussio-Fournier, J. C.
Fowell, D. M., 397
Fowler, E. F., 452
Fowler, W. S., 475, 477, 484
Fox, C., 475
Fox, C. A., 143
Foxon, G. E. H., 391
Fradkin, M. V., 246
Frame, B., 90
France, H. O., 536
Franck, C., 69, 480
Frank, E., 126
Frank, H. A., 92, 512
Frank, K., 574, 575, 576, 577, 578, 580
Frankel, R., 439
Frankl, W., 84
Franklin, A. L., 338, 340, 341
Franklin, K. J., 388, 451, 496
Frantz, I. D., Jr., 72
Frantz, M., 86
Frantz, R., 252
Frazer, A. C., 122, 123
Fredericq, H., 417
Freed, M., 358
Freedberg, A. S., 446
Freeman, G. L., 269
Freeman, H., 371
Freeman, L. W., 93, 143
Freeman, M. L. H., 376, 379
Freeman, S., 85, 87, 510
Freeman, W., 162, 272
Freis, E. D., 452, 573
Fremont-Smith, P., 368
French, C. R., 447
French, D. M., 446
French, G. N., 570
French, J. D., 163, 164, 208
French, T. H., 51, 65
Frenchman, R., 121
Freud, J., 35
Frey, T. S., 199
Freyburger, W. A., 568, 569, 570, 571
Frey-Wyssling, A., 555
Frick, J. D., 574, 575, 577
Fried, P. H., 34, 35
Friedberg, F., 71, 72
Frieden, J., 374, 375
Friedgood, C. E., 89
Friedgood, H. B., 38, 364
Friedland, C. K., 410, 443
Friedlander, R. D., 83
Friedman, C. L., 451
Friedman, M., 505, 509
Friedman, M. H. F., 86, 113, 114, 116, 117, 124, 130
Friedman, S. M., 451
Friend, F. J., 69
Friesen, S. R., 127
Frilley, M., 13
Frisk, A. R., 61, 567
Frital, D., 218
Fritz, J. C., 11
Froeschels, E., 242
Fröhlicher, R., 324
Frommel, E., 418, 560
Frommeyer, W. B., 338, 340
Fruton, J. S., 360
Fry, E. G., 366, 370
Fry, G. A., 248, 249, 251, 255, 256, 258, 259
Fugo, N. W., 6, 27
Fuhrman, F. A., 183
Fuller, F. D., 327
Fuller, P. E., 215
Fulton, J. F., 162, 163, 165, 208, 270
Funkenstein, O., 208
Fuortes, M. G. F., 221
Furchgott, R. F., 438, 449
Furrer, W., 235
Furth, J., 358
Furuta, W. J., 362
Fuster, B., 166
Futcher, P. H., 496

G

Gabor, D., 233
Gabrici, E., 478
Gabrio, B. W., 6
Gad, I., 89
Gaddum, J. H., 146, 327
Gaensler, E. A., 578
Gaida, 84
Gajdos, A., 86
Gajdos-Torok, M., 86
Galambos, R., 232, 235
Galdston, M., 476, 481
Galifret, Y., 253
Gallagher, C. D., 258
Gallagher, J. R., 258
Gallego, A., 181
Gallera, J., 15
Galli-Mainini, C., 35
Gallien, L., 35
Gambill, E. E., 111

Gammon, G. D., 327
Gantt, W. H., 483
Garb, S., 409
Garber, M. J., 7
García Ramos, J., 392, 393, 410, 417
Gardner, E., 168, 269
Gardner, G., 60
Gardner, J. E., 473
Gardner, M., 241
Garfinkel, A., 124
Garner, W. R., 240
Garofalo, F., 327
Garrey, W. E., 394
Garst, J. B., 38
Garthwaite, B., 471
Garton, G. A., 31
Garvin, J. S., 217
Gasic, G., 366
Gassner, F. X., 56
Gast, J. H., 416
Gastaut, Y., 208, 210, 219
Gastineau, C. F., 66
Gaston, E. A., 64
Gaston, E. O., 533
Gát, L., 249
Gates, M., 338
Gattone, V., 484
Gatty, O., 551
Gaudry, R., 344
Gaunt, W. E., 147
Gaus, J., 256
Gaustaut, H., 201, 208, 210, 218, 219, 222
Gavrilesco, E., 372, 374
Gaylor, J. B., 193
Geets, W., 188
Geever, E. F., 407
Geger, J. H., 538
Geiling, E. M. K., 411
Geisinger, R., 378
Gellhorn, E., 154, 161, 163, 207, 208, 212, 221, 260, 327
Gemmill, C. L., 47, 476
Gentling, A. A., 575, 579
George, W. L., 340
Geraci, J. E., 477, 484
Gerard, R. W., 184, 195, 327, 484
Gerbode, F., 390
Gerebtzoff, M. A., 206
Gerendás, M., 312
Gerhardt, J. W., 221
German, H. L., 7
Germuth, F. G., Jr., 88, 89
Gernandt, B., 143, 144, 251, 396
Gertler, M. N., 391
Ghormley, R. K., 453
Ghosh, N. C., 63
Giansiracusa, J. E., 448
Giarman, M. J., 416
Gibbon, M. H., 475
Gibbons, T. B., 401
Gibbs, E. L., 166, 200, 218, 221
Gibbs, F. A., 166, 199, 200, 201, 215, 216, 218, 221
Gibson, J. G., 436, 440
Gibson, L. H., 414
Gierke, H. von, 470
Gilbert, C., 25
Gilchrist, M., 477
Gilder, H., 90, 335, 336
Giles, N. H., Jr., 530
Gilger, A. P., 251, 255
Gille, R., 374
Gilliatt, R. W., 152, 443, 474
Gillick, F. G., 390
Gillis, M. O., 5
Gillman, J., 25, 84
Gillman, T., 56, 84, 87, 355
Gilman, A., 214, 327, 469, 506
Gilman, A. J., 184
Gilman, T., 120, 121
Gilson, A. S., Jr., 298, 301, 302, 305, 310, 323, 395
Gilson, W. E., 214, 308, 408
Gineste, P. J., 149
Gingras, R., 344
Ginsberg, R. S., 104
Ginzler, A. M., 214
Giraldi, E., 439
Girard, O., 12
Girden, E., 215, 292
Girdwood, R. H., 338, 339
Giroud, A., 71
Gjessing, E. C., 374
Glantz, P. J., 33
Glass, G. B. J., 113
Glass, S. J., 90
Glasser, O., 92
Glassman, L., 574
Glenny, I. H., 405
Glick, D., 72
Globus, J. H., 70
Glomset, D., 387, 389
Glotzer, S., 63
Glynn, J. H., 509
Glynn, L. E., 86, 87, 88
Gobat, Y., 413
Godbey, M. E., 327
Godeaux, J., 313
Godet-Guillain, J., 208
Godet, R., 26
Goetz, R. H., 458, 572
Goetzl, F. R., 103
Goffart, M., 304, 305, 313
Gold, J. J., 398, 459
Gold, M. A., 517
Gold, P., 560
Goldberg, H. H., 408
Goldblatt, H., 86, 450
Goldenberg, M., 573
Goldensohn, E. S., 478
Goldfarb, A. I., 70
Goldfeder, A., 470, 533
Goldinger, J. M., 346
Goldman, L., 214
Goldman, M. L., 455, 496
Goldmann, H., 256
Goldring, W., 453
Goldsmith, E. D., 344
Goldwater, W. H., 8
Gollan, F., 450, 478, 484
Gollwitzer-Meier, K., 479, 480
Golseth, J. G., 327
Gomez, C. A., 390
Gomez, D. M., 506
Gomori, G., 21
Gonzalez-Oddone, M. V., 94, 356
Gonzalez Q., J., 415
Good, D. R., 484
Goodale, W. T., 400, 401, 406, 448
Goodall, H. I., 339
Goodall, J. W. D., 339
Goodell, J. P. B., 538
Goodman, J., 216, 439, 474, 498
Goodman, L. S., 212, 214, 569
Goodman, S. C., 505
Goodpaster, W. E., 512
Goodwin, J. E., 218
Goodwin, J. F., 59
Goodwin, L. G., 146
Goormaghtigh, N., 440
Göpfert, H., 298, 301
Goranson, E. S., 48, 59
Gorbman, A., 61, 538
Gordan, G. S., 52, 71, 572
Gordon, A. R., 551
Gordon, A. S., 68, 343
Gordon, D. A., 256
Gordon, G. S., 577, 579
Gordon, I., 454
Gormsen, H., 378

Gornall, A. G., 119
Göthlin, G. F., 179, 250
Gottlieb, J. S., 216, 222
Gottlieb, O., 66, 372
Gough, N., 27
Gould, J. C., 113
Gould, R. G., 478
Govier, W. H., 510
Govier, W. M., 419, 420
Grabar, P., 35
Graef, I., 367
Graetzer, E., 68
Graevskaya, B. M., 536
Graf, C., 208, 211
Graf, L. H., 358
Grafflin, A. L., 94
Graham, G., 470
Graham, H. T., 179
Grahame, D. C., 553
Graham-Service, D. M., 327
Grailly, R. de, *see* de Grailly, R.
Grandpierre, R., 69, 480
Granger, H. R., 456, 457, 470
Granick, S., 120, 335, 336, 344
Granit, R., 247, 251
Grant, F. C., 252
Grant, R., 483
Grant, W. C., 346, 477, 484
Grass, A. M., 201
Grau, S., 410
Grauer, H., 414
Gray, C. H., 93
Gray, F. D., Jr., 398, 400, 471
Gray, J. S., 108
Gray, L. H., 530
Gray, P., 10
Graybiel, A., 256
Greco, G., 477
Greeley, P. O., 62
Green, D. M., 290, 440
Green, H. D., 439, 440, 503, 567
Green, J. D., 35, 155
Green, M. H., 495
Greenbaum, A. L., 29, 51, 65
Greenberg, D. M., 71, 72, 510
Greenblatt, M., 156, 208
Greene, J. D., 71
Greene, R. R., 24
Greenhill, J. P., 36
Greening, J. R., 528
Greenstein, J. P., 528
Greenwald, I., 55
Greep, R. O., 69
Greer, C. M., 146
Gregersen, M. I., 104, 402, 437, 440
Gregg, D. E., 405
Gregg, D. J., 405
Gregg, J. R., 556
Gregg, N. M., 7
Grégoire, C., 364, 368, 378
Grégoire, F., 400, 448
Gregor, H. P., 553
Gregory, R. A., 112, 125
Greif, R., 505
Greiff, D., 11
Greisheimer, E. M., 118, 470
Grelis, M. E., 419, 420
Grenell, R. G., 212
Grether, W. F., 258
Greville, G. D., 199, 202, 204, 216, 222
Grezes-Rueff, C., 221
Grezes-Rueff, F. A., 221
Grieg, M. E., 518, 579
Griesbach, W. E., 54, 60
Griffin, D. R., 249, 253
Griffith, J. Q., Jr., 533
Griffiths, M., 68
Grigger, R. P., 85
Grimes, R., 167
Grimm, E., 376
Grimson, K. S., 125, 448, 451
Grindlay, J. H., 91, 117, 118, 129
Grinstein, M., 335, 336, 345
Grisell, T. L., 125
Grob, D., 341
Groedel, F. M., 410
Groen, J., 88, 121, 123
Groff, A. E., 92, 442
Grollman, A., 27, 451
Grönwall, A., 30
Groom, D. L., 477
Gross, A., 370
Gross, D., 396
Gross, E., 417
Gross, E. G., 574, 576, 579
Gross, F., 418
Gross, J., 54, 61
Grossman, M., 396, 441, 469
Grossman, M. I., 89, 104, 111, 112, 116, 127, 129
Grossman, N., 388, 391
Grove, J., 259
Gruber, C. M., 484
Grubin, A. F., 528
Gruenstein, M., 128
Gruhzit, O. M., 458, 566
Grumbach, L., 304
Grundfest, H., 144, 173, 174, 184, 185, 199, 213, 297, 309
Gualtierotti, T., 202, 206, 207
Guarneri, V., 573
Guba, F., 311
Gubner, R., 444
Guensberg, E., 555, 557
Guerra, F., 414
Guerrero, R. D., *see* Diaz-Guerrero, R.
Guest, M. M., 126, 415, 441, 457
Guggenbühl, A., 256
Guibovick, C., 410
Guild, R., 71
Guild, S. R., 234, 236
Guillain, J. G., *see* Godet-Guillain, J.
Guillemot, E., 249
Guilly, P., 222
Gukelberger, M., 494, 505, 506, 511
Gump, H., 346
Gundelfinger, B. F., 448
Gunn, F. D., 85
Gunton, R., 495
Gurchot, C., 28
Gurd, F. N., 89
Gurin, S., 70
Gustafson, G. E., 513
Gustavson, R. G., 56
Guterman, H. S., 27
Guth, E., 298, 299, 306, 321, 322, 323
Guthrie, J. S., 365
Gutman, E., 327
Gutmann, J., 113
Guttman, L., 153
Guttman, S. A., 218, 304, 307
Guttmann, L., 443, 474
Guyton, A. C., 484
György, P., 56, 85, 86, 88, 90
Györgyi, A. S., *see* Szent-Györgyi, A.

H

Haag, H. B., 578, 579, 580
Haas, H. T. A., 52
Habel, K., 7

Hack, M. H., 69, 149
Haddow, A., 368
Hadidian, Z., 2, 32
Hafkenschiel, J. H., 401, 406, 415
Hafner, P. G., 327
Hagen, C. W., Jr., 531
Hahn, L., 357
Hahn, P. F., 120, 121, 397, 517, 538
Haig, C., 253
Haig, E. M., 253
Haimovici, H., 570
Haines, S. F., 61
Hainsborough, L. A., 5
Haist, R. E., 48, 62
Hajek, N. M., 327
Hald, P. M., 555, 556, 557
Hale, E., 112
Hall, B. E., 338
Hall, C. E., 104, 298, 311, 312, 315, 319
Hall, F. G., 478
Hall, K., 28
Hall, V. E., 327, 412, 416, 483
Hall, W. K., 245
Hallden, U., 248, 260
Hallenbeck, G. A., 112
Hallpike, C. S., 234
Halminen, E., 410
Halperin, M. H., 443
Halpern, B. N., 470
Halpert, B., 94
Halpin, J. G., 5
Halse, T., 69
Halstead, W. C., 162, 218, 273
Ham, W. E., 30
Hamburger, J., 470
Hamburger, V., 7, 16
Hamil, B. M., 8
Hamilton, A. S., 440
Hamilton, C. E., 26
Hamilton, H. C., 293
Hamilton, J. B., 37
Hamilton, J. E., 48
Hamilton, J. G., 527
Hamilton, P. B., 439, 440, 494, 500, 501, 509, 512, 513, 516, 518, 519
Hamilton, W. F., 397, 398, 399, 459
Hamilton, W. G., 397
Hamilton, W. M., 341
Hammer, J. M., 128, 130
Hammond, J., 36
Hammond, W. S., 15, 16, 140
Hampel, C. W., 156
Hampson, J. L., 161, 164, 165, 239
Hanafin, M., 195
Hancock, J. L., 23
Handelsman, J. C., 400, 448
Handler, P., 57
Haney, H. F., 148
Hänni, H., 552
Hanrahan, E. M., 129
Hansen, R. G., 12, 30
Hansen-Pruss, O. C., 338
Hanson, M. E., 104
Hara, M., 472
Harboe, N., 66
Hardenbergh, E., 355, 356, 360, 473
Hardwick, C., 453
Hardy, L. H., 258
Hardy, W. G., 242
Hare, K., 499, 505
Hare, R. S., 499, 505
Harkins, H. N., 119, 128, 130, 368
Harlow, H. F., 270, 271, 273
Harmel, M. H., 401, 406, 415
Harmon, P. J., 247
Harned, H. S., 551
Harper, A. A., 116
Harper, H. A., 85
Harper, W. I., 390
Harpuder, K., 443
Harrell, G. T., 245
Harrell, R. F., 293
Harrington, D. O., 260
Harris, A. D., 84
Harris, A. S., 392, 393, 395, 410, 414, 440
Harris, D. L., 327
Harris, G. W., 35, 71, 155, 364
Harris, J. D., 241
Harris, M., 23
Harris, P. L., 327
Harris, R. S., 121
Harris, S., 372
Harris, S. C., 69, 104
Harris, T. N., 376, 377, 378, 379
Harrison, C. R., 164
Harrison, H. C., 88
Harrison, H. E., 440, 517
Harrison, R. G., 15
Harrison, R. J., 26
Harrison, T. R., 403, 423
Hart, E. B., 344
Hart, E. R., 89
Hart, G. H., 23
Hart, W. M., 245
Harter, B. T., 21, 23
Hartline, H. K., 250, 251
Hartman, E., 257
Hartman, F. A., 65
Hartree, E. F., 554, 555
Hartridge, H., 247, 249, 252, 258
Harvey, A. M., 341
Harvey, R. A., 535
Harvey, R. B., 469, 496
Harvies, L. C., 414
Haslewood, G. A. D., 27
Hasman, M., 553
Hasselquist, H., 357
Hastings, A. B., 478
Haugaard, N., 48
Haushalter, E., 327
Hausman, D., 116
Havard, R. E., 515
Havens, W. P., Jr., 83
Hawkins, J. E., 235, 241
Hawkins, J. E., Jr., 439
Hawkins, R. D., 341
Hawkins, V., 338
Hawkinson, V., 93
Hawley, G., 92
Haxton, H. A., 327
Hay, E. C., 66, 416, 510
Hayes, K. J., 280
Haymaker, W., 214
Haynes, F. W., 355, 448, 449, 453, 473
Hays, E. E., 343
Hayward, G. W., 566
Hazard, R., 418, 484
Heagan, B. S., 477, 484
Heard, R. D. H., 49
Hebb, C., 194, 473
Hébert, S., 49
Hecht, L., 9
Hecht, S., 254, 255, 258
Hechter, O., 2, 32, 364, 370
Hector, O., 47
Hedenstedt, S., 560
Heemstra, H., 472, 476, 478, 484
Heerhaber, I., 479
Heersma, J. R., 123
Hege, J. R., Jr., 503
Hegglin, R., 414
Hegnauer, A. H., 174, 442, 473
Hegsted, D. M., 121
Heide, E. C. V., *see* Vonder Heide, E. C.

Heil, J. F., 442
Heilbrunn, L. V., 305, 318, 319, 327
Heilman, D. H., 364
Heimburger, R. F., 143, 390
Heinbecker, P., 70, 399, 416, 453, 504
Heineman, S. D., 575
Heinemann, M., 53
Heinle, R. W., 338, 340, 368
Heinrich, R. A., 340
Heinsen, A. J., 555, 557
Heiskanen, L. B., *see* Bastman-Heiskanen, L.
Hekker, T., 547, 549, 552
Hellebrandt, F. A., 327
Hellems, H. K., 448
Heller, C. G., 34, 38
Heller, H., 120, 499
Heller, J. H., 449, 450, 455
Hellerstein, H. K., 389
Hellman, L., 370
Hellman, L. M., 28
Helm, J. D., Jr., 118
Helmer, O. M., 450
Helson, H., 259
Hemingway, A., 475, 478, 484
Hempelmann, L. H., 367, 533, 535
Hemphill, R. E., 67
Henderson, F. F., 578
Henderson, F. G., 579
Henderson, J. E., 27
Henderson, J. W., 164, 248, 250
Henderson, L., 201, 208
Hendley, C. D., 255
Hendrix, J. P., 568
Henle, W., 372
Henneman, E., 162, 164, 165
Henny, G. C., 217, 390
Henry, C. E., 203
Henry, J., 439
Henry, J. P., 473, 474, 498
Henry, K. M., 30
Henry, R., 477
Henschel, A., 106, 447
Henshaw, P. S., 530, 531, 535
Heppenstall, M., 199, 202, 204, 216
Herber, F. J., 478
Herbert, P. H., 84
Herlihy, W. F., 446
Herlitzka, A., 469
Hermann, H., 153
Hermans, J. J., 552
Herr, R., 410
Herraiz, M. L., 124
Herrick, C. J., 165
Herrin, R. C., 504
Herrmann, H., 9
Hershenson, B. B., 574
Hertig, A. T., 21, 36
Hertz, G., 550
Hertz, R., 38
Hertzman, A. B., 443
Hess, W. C., 11, 122
Hess, W. R., 483
Hesser, F. H., 125
Heston, W. E., 530, 531
Heuser, G. F., 5, 341
Heyer, H. E., 403, 410, 423, 469
Heymans, C., 221, 451, 471, 480, 484
Hiatt, E. P., 499
Hibbs, R. E., 59, 90
Hickam, J. B., 400, 402, 472
Hiestand, W. A., 327
Higgins, E. L., 248
Higgins, G., 90
Higgins, G. C., 249, 255
Hildreth, H. R., 249
Hill, A., 407
Hill, A. V., 300, 302, 303, 307, 318, 320, 325, 326
Hill, D., 199, 201, 202, 203, 204, 208, 216, 217, 218, 219, 223
Hill, D. L., 184
Hill, E. J., 128, 130
Hill, F. C., 129
Hill, H. C., 448
Hill, R. F., 410
Hill, R. T., 22, 23
Hillap, N-Å., 21, 34
Hiller, A., 440, 512, 513, 518, 519
Hills, A. G., 68, 370, 374
Hilsabeck, J. R., 129
Himmelstein, A., 397, 400, 410, 471, 472
Himsworth, H. P., 83, 84, 86, 87, 88
Himwich, H. E., 415
Himwich, W. A., 415
Hinchey, J. J., 453
Hinds, E. G., 517
Hines, E. A., Jr., 453
Hines, H. M., 59, 327, 359, 444
Hines, M., 161
Hinglais, H., 35
Hinglais, M., 35
Hingson, R. A., 444
Hirsch, G., 537
Hirsch, M. J., 249, 257
Hirsh, S. A., 575, 577, 579
Hisey, A., 518
Hitchcock, F. A., 469, 476, 484
Hitchings, G. H., 340
Hoag, A., 327
Hoagland, C., 327
Hoaglund, C. L., 83, 84, 85, 90, 91
Hoaglund, H., 201, 222, 304
Höber, R., 307, 552
Hoberman, H. D., 361, 375
Hodel-Boos, M., 256
Hodes, R., 327, 482
Hodges, F. J., 567
Hodges, P. C., 390
Hodgkin, A. L., 177, 178, 181
Hoefer, P. F. A., 217, 218
Hoeflich, E. A., 447
Hoelzel, F., 104
Hoessly, G. F., 248
Hoff, H. E., 391, 417
Hoffbauer, F. W., 85, 86, 91
Hoffman, A. C., 259
Hoffman, E. J., 150, 416
Hoffman, J. C., 535
Hoffman, M. M., 123
Hoffman, R., 124
Hoffmann, E. J., 56
Hoffmann, F., 56, 150, 416
Hoffmeyer, J., 89
Hofstetter, T., 109
Hogan, A. G., 344
Högberg, B., 357
Hogeboom, G. H., 413
Hogg, J. A., 63
Hokin, L. E., 109, 558
Hollaender, A., 528
Hollan, S., 115
Holland, H. L., 576
Hollander, F., 110, 112
Hollander, W. F., 5
Holldack, K., 473
Hollinshead, W. H., 33, 35, 36, 151, 154
Holman, E., 390
Holman, H., 360
Holman, J., 469
Holman, R. L., 458

Holman, W. I. M., 8
Holmes, J. H., 104, 437, 509
Holmes, P. E. B., 566
Holmgren, B. S., 391
Holmgren, H., 61
Holt, J. F., 567
Holt, L. E., Jr., 85
Holt, M., 559
Holtfreter, J., 15
Holzer, W., 391
Holzmann, E. M., 125
Homburger, A., 415
Homburger, F., 66, 85, 361
Høncke, P., 217, 218, 298, 300, 306
Hoobler, S. W., 458, 566, 567, 568, 569
Hooker, C. W., 30, 90
Hooker, D. H., 128, 130
Hooper, K. Z., 457
Hooton, T. C., 91
Hopkins, F. H., 376, 379
Hoppe, J. O., 579
Hopson, J. L., 476, 481
Horeau, A., 30
Horecker, B. L., 413
Horlick, L., 393
Horner, R. G., 258
Horning, E. S., 33, 365
Horowitz, M. W., 282
Horst, L. van der, *see* van der Horst, L.
Horsten, G. P. M., 191
Horstmann, P., 109
Horton, F. H., 455
Horton, R. G., 304
Horvath, S. M., 327
Horwitz, S. A., 476
Hotchkiss, R. D., 413
Hough, V. H., 85
Hounie, E., 376
Houssay, H. E. J., 359
Houtz, S. J., 327
Hove, E. L., 327
Howard, F. H., 390
Howard, H. W., 11
Howard, J. E., 73
Howarth, S., 400, 401, 402, 472
Howell, C. E., 23
Howland, J. W., 532
Hsia, Y., 258
Hsu, C. Y., 7
Hubacher, O., 391
Hubbard, R , 253
Huber, A., 246
Huber, D., 27
Huddleston, O. L., 327
Hudgins, C. V., 241
Hudson, L., 51
Heuper, W. C., 87, 390, 518
Huf, E., 327
Huff, E. G., 327
Huffman, H. M., 495
Hughes, E. S. R., 140
Hughes, J. S., 13
Hugh-Jones, P., 327
Huguley, C. M., 337, 345
Huidobro, F., 122
Humbert, R., 308
Humerez, J., 34
Humm, D. G., 391
Humm, F. D., 90
Hummel, J. P., 327
Humphreys, E. M., 91
Humphreys, R. J., 147, 417
Humphreys, S. R., 345
Hunt, C. C., 84, 571
Hunt, J. McV., 288
Hunt, M. L., 345, 346
Hunt, R., 565
Hunter, F. R., 554, 555
Hunter, J. A., 476, 484
Hunter, M. K., 554
Hupsel, O., 246
Husby, J., 59
Huskins, C. L., 3
Hutaff, L., 346
Hutchens, T. T., 372
Hutchings, B. L., 341
Huxley, A. F., 178
Hwang, K., 106

I

Iglesias, R., 34
Ing, H. R., 565
Ingall, F., 442
Ingelfinger, F. J., 92, 104, 118, 442
Ingle, D. J., 63, 64, 65, 68, 71
Ingram, W. R., 163
Inman, V. T., 298, 302, 306
Innes, E. M., 338, 339
Irvin, J. L., 94
Irving, L., 477, 484
Isbell, H., 574, 575, 576, 577, 578, 580
Ishimoto, M., 250
Ishmael, W. K., 574, 579
Isola, W., 141
Israel, F. W., 576, 577, 580
Ivanoff, A., 249, 253, 255
Ivanoff, N., 308, 555, 557
Ivanov, D. I., 126
Ivy, A. C., 87, 89, 104, 107, 114, 117, 120, 121, 126, 127, 327, 355
Ivy, J. H., 474

J

Jaarma, M., 357
Jablons, B., 457
Jackson, R. L., 390
Jackson, S., 94
Jacob, J., 308, 313, 471, 480, 484
Jacob, L., 12
Jacobs, E. C., 90
Jacobs, H., 473
Jacobs, H. J., 475, 484
Jacobs, J. E., 518
Jacobs, M. H., 550, 551, 554
Jacobsen, E., 342
Jacobson, L. O., 371, 530, 531, 532, 533, 537
Jacoby, F., 89
Jacques, J., 30
Jaeger, A., 247, 249
Jaeger, L., 9
Jager, V. B., 367
Jahan, I., 508
Jahn, T. L., 251
Jakus, M. A., 298, 311, 312, 315, 319
Jalavisto, E., 253
Jalling, D., 113
Jalling, O., 89
James, H. P., 579
Janes, R. G., 62
Janouch, M., 511
Janssen, L. W., 552
Janton, O. H., 478
Jaques, L. B., 441
Jaques, S., 308
Jasper, D. E., 127
Jasper, H. H., 161, 166, 167, 199, 201, 205, 208, 211, 220, 221, 327
Javier de Elio, F., *see* de Elio, F. J.
Jeanneret, R. L., 252
Jefferson, N. C., 107, 130
Jellinek, E. M., 86
Jenden, D. J., 566
Jenkin, L., 257
Jenney, E. H., 574, 579

Jensen, K. K., *see* Kjerulf-Jensen, K.
Jepson, R. P., 567
Jersild, M., 90
Jochim, K., 415
Jochim, K. E., 443
Johansmann, R. J., 406
John, E. S., 367, 535
John, H. M., 66, 375, 377
Johnson, A. L., 400
Johnson, B. C., 340
Johnson, C., 86
Johnson, C. A., 445
Johnson, F. A., 121
Johnson, H. C., 214
Johnson, H. T., 577
Johnson, J. R., 92
Johnson, R. B., 341
Johnson, R. E., 214
Johnson, R. M., 57, 85
Johnson, V., 107
Johnson, W. H., 341
Johnston, B. J., 495
Johnston, C. G., 94
Johnston, D. L., 200
Johnston, F. D., 410
Jolliffe, N., 86
Jones, A. M., 399
Jones, B. F., 341
Jones, C. M., 91, 119, 567
Jones, E., 338
Jones, F. N., 279
Jones, H. P., 421
Jones, L. A., 249, 255
Jones, M. J., 340
Jones, P. H., *see* Hugh-Jones, P.
Jones, R., 573
Jones, R. C., 235
Jones, R. N., 38, 512
Jones, R. P., 367
Jonxis, J. H. P., 13
Jope, H. M., 477
Jordan, J. R., 304
Jordan, W. K., 312, 315, 316
Jorpes, E., 113
Josefsson, E., 61
Josephson, B., 505
Joslin, E. P., 50
Jost, A., 14, 33, 38
Jost, M. A., 14
Joyce, H. E., 90
Jucker, S., 557
Judd, D. B., 252
Jukes, T. H., 338, 339, 340, 341
Jung, R., 222
Jungck, E. C., 34
Junge, J., 495
Jungeblutt, C. W., 222
Junqueira, L. C. U., 105

K

Kahler, O., 235
Kahn, J., 7
Kahn, R. H. B., *see* Broh-Kahn, R. H.
Kahrman, R., 399
Kaiser, E., 298
Kaiser, I. H., 24, 26
Kaiser, R., 575
Kalckar, H. M., 49, 312, 325, 340
Kalman, C., 51
Kamell, S. A., 24
Kamen, M. D., 335, 527
Kaniowski, W., 255
Kantor, J. R., 270
Kaplan, H. S., 359
Karczmar, A. G., 305
Karel, L., 476, 478
Kark, R. M., 214
Karlin, J. E., 241
Karnofsky, D. A., 367
Karp, D., 110, 111
Karplus, S., 258
Karr, N. W., 572, 577
Karstens, A., 473
Karvonen, M. J., 479
Kaser, M. M., 338
Katherman, R. E., 30, 555, 557
Katz, B., 188, 308, 309
Katz, E. J., 533
Katz, J., 114, 128, 249
Katz, L. N., 69, 152, 388, 395, 399, 407, 410, 415, 458, 469, 473, 570
Katzman, P. A., 35
Kaucker, M., 8
Kaufman, I. C., 217, 221, 222
Kaufman, W., 408
Kaulbersz, J., 114
Kaunitz, P. E., 406
Kaylor, C. T., 387, 388
Keaster, J., 241
Keating, F. R., Jr., 61
Keating, R. P., 407
Keele, C. A., 512
Keen, J. A., 388
Keighley, G., 511
Keilin, D., 554, 555
Keilina, R. Ya., 536
Keith, N. M., 495
Keleman, G., 241
Kellaway, P., 235
Keller, A. D., 70
Keller, R., 109
Kelley, V. C., 63, 370, 374, 376
Kellner, A., 454
Kelsall, A. R., 90
Kelsey, M. P., 305
Kemmerr, K. S., 85
Kemp, C. R., 444
Kemp, T. A., 339
Kendall, F. E., 83, 454
Kennard, M. A., 156, 202, 218
Kennedy, J. L., 327
Kennedy, T. H., 54
Kennedy, T. J., Jr., 506
Kenney, R. A., 69, 456, 497, 506
Kenyon, A. T., 67
Kerr, L. M. H., 72
Kershman, J., 199
Kershner, D., 91
Kersten, H., 448
Keston, A. S., 566
Keys, A., 106, 259, 447, 493
Khalil, F., 496
Khynova, A. U., *see* Uxova-Khynova, A.
Kibbe, M. H., 222
Kielley, W. W., 314
Kimball, S., 85
Kimble, L. L., 222
Kindred, J. E., 367
King, E. J., 477
King, E. N., 113, 116
King, H. K., 113
King, R. B., 161, 165
Kinney, T. D., 121
Kinsell, L. W., 85
Kinsey, A. C., 38
Kinsey, V. E., 247, 495
Kipple, H. M. 412
Kirchhof, A. C., 574, 576, 577, 579, 580
Kirchhof, J. K. J., 327
Kirillov, N. I., 552
Kirkpatrick, B. B., 215, 219, 222
Kirschbaum, A., 368
Kirsner, J. B., 114
Kisch, B., 69
Kisieleski, W. E., 537
Kisker, G. W., 272
Kitchin, W. W., 125
Kitzmiller, K. V., 494
Kjeldgaard, N. O., 340
Kjerulf-Jensen, K., 358

Klatskin, G., 90
Klein, E. E., 304
Klein, J. R., 63, 214
Kleinzeller, A., 315, 323
Klemme, R. M., 142
Klenow, H., 340
Kline, L. H., 327
Kline, L. L., 86
Kline, R. F., 447
Klingler, K., 56
Kliorin, A. I., 105
Klotz, M. O., 30
Knappeis, G. G., 298, 317, 324
Knisely, M. H., 91, 459
Knodt, C. B., 32, 33
Knoll, H. A., 248
Knott, J. R., 163, 216, 222
Knouff, R. A., 65
Knowlton, K., 67
Knowlton, N. P., Jr., 535
Knox, G. W., 218
Knudsen, O. S., *see* Sten-Knudsen, O.
Kobrak, H. G., 232
Kochakian, C. D., 38, 50, 455
Koechlin, A. L., *see* Lerique-Koechlin, A.
Koella, W., 250
Koelle, G. B., 184, 327, 418
Koenig, H., 473
Koenig, R., 473
Koestler, W., 552
Köhler, W., 257
Kohlstaedt, K. G., 576, 577, 580
Kohn, H. I., 252
Kohrman, R. M., 143, 482
Kolb, L. C., 221
Koletsky, S., 513
Kollros, J. J., 214
Komarov, S. A., 113, 128
Kometiani, P. A., 304
Kon, S. K., 29, 30
Kondo, B., 152, 388
Kondritzer, A. A., 8
Koomen, M. J., 248, 249
Koop, C. E., 85
Koopman, L. J., 191
Kopeloff, L. M., 222
Kopeloff, N., 222
Koppanyi, T., 569
Kornberg, A., 413
Kornmüller, A. E., 199
Koropov, V. M., 105
Korr, I. M., 327
Kortsák, A. S., *see* Sass-Kortsák, A.
Kosman, A. J., 327
Kosmo, L. S., 6
Kossman, C. E., 408, 410
Kosterlitz, H. W., 88
Kottke, F. J., 451, 496
Kowalewski, K., 110
Kozy, J. S., 91
Krahl, M. E., 47
Krahl, V. E., 398
Krall, L. P., 50
Kramer, B., 124
Kramer, P., 118
Kramer, W., 48
Kramke, E. H., 11
Krapcho, J., 575
Krasnovskaya, L. A., 105
Kratz, J. D., 249
Krause, A. C., 247, 251
Krayer, O., 416
Krebs, E. T., 28
Krebs, E. T., Jr., 28
Kreiger, V. I., 453
Kreindler, A., 217
Kreiss, R. E., 68, 70
Kremer, V. L., 476, 481
Kremer, W. F., 156, 162
Krems, A. D., 327
Kreula, M. S., 124
Krichesky, B., 33, 90, 367
Krieg, W. J. S., 162
Kriss, J. P., 496
Krogh, A., 342
Kronenberg, G., 203
Krop, S., 309, 341, 456
Kruger, H. E., 405, 407
Kruhøffer, P., 494
Kruyt, W., 478
Kryter, K. D., 237
Kryvi, 12
Kubicek, W. G., 451, 475, 496
Kuffler, S. W., 195, 293, 309
Kugelberg, E., 327
Kugelberg, I., 258
Kuizenga, M. H., 64
Kumpe, C. W., 110
Kun, E., 419
Kunkel, A. M., 341
Kunkel, H. G., 83, 84, 85, 91
Kuntz, A., 140, 141, 142, 143, 248
Kunze, D. C., 406
Kurland, A. A., 222
Kurshakov, N. A., 478
Kurtz, L. D., 109
Kurzrok, R., 2, 31, 32, 53
Kuzell, W., 60

L

Labat, J. C., *see* Ceballos Labat, J.
Labby, D. H., 84, 85, 90, 91
Labhart, H., 246
Labouche, C., 118
Lacape, R. S., 202
Lachman, P. O., 116
Lackey, R. W., 414
Ladd, A. T., 454
La Due, J. S., 573
Lagerlöf, H. O., 116
Laker, D. J., 451
Lalich, J. J., 517
Lamar, E. S., 255
Lambert, E. H., 305, 566
Lambie, C. G., 475, 484
Lambie, M. W., 88
Lamotte-Barrillou, S., 59
Lamotte, M., 59
Lampen, J. O., 340
Lamson, B. G., 88
Lamson, P. D., 495, 518
Lamy, M., 59
Landau, R. L., 67
Landauer, W., 6
Landboe-Christensen, E., 115, 341
Landis, E. M., 356, 398, 451, 477, 484, 560
Landmesser, C. M., 401, 406, 415, 471
Landowne, M., 452, 494
Lands, A. M., 456, 457, 470
Landulfo, J., 410
Lane, J. D., 91
Lang, E. P., 560
Lange, J., 510, 516
Lange, K., 445
Langendorf, R., 395
Lapides, J., 567, 578
Laplane, R., 200, 216, 218
Laporte, Y., 195, 303
Laqueur, G., 60
Lardy, H. A., 59
Laroche, C., 327
Larrabee, M. G., 162, 193, 194, 482
Larralde, J., 122
Larsell, J. F., 233
Larsell, O., 233
Larson, E. A., 93, 335

Larson, P. S., 578, 579, 580
Larsson, Y., 567
Lashley, K. S., 238, 277
Lasón, R. L., *see* Limón Lasón, R.
Last, S. L., 222
Lathrop, K. A., 537
Latner, A. L., 60
Latta, H., 473
Latta, J. S., 368, 369, 372
Lauber, F. U., 112
Lauener, H., 555, 557
Laufer, M. W., 217, 218
Laurell, C. B., 345
Laursen, T., 89
Lauson, H. D., 400, 402
LaVelle, F. W., 26
Lavietes, P. H., 556
Lavin, G. I., 359
Law, L. W., 364, 368
Lawrence, A. S. C., 315, 323
Lawrence, J. H., 527
Lawrence, J. S., 370, 371, 373, 533, 534
Lawrence, J. W., 534, 539
Lawrence, K. G., 6
Lawson, A., 60
Lawson, H. C., 435, 436
Lawson, J. D., 106
Lawson, R. N., 110
Lawson, R. W., 254, 259
Layani, F., 56
Layne, J. A., 90
Layton, A., 248
Lazovik, A. D., 285
Leão, A. A. P., 206
Lear, P., 531
Leary, J. S., 421
Leath, M. J., 52
Leathem, J. H., 58
Leblond, C. P., 54, 61, 103, 366, 538
Le Breton, E., 116
Lederer, J., 121
LeDuc, E. H., 88
Lee, A. J., 162
Lee, D., 447
Lee, H. M., 578
Lee, J., 575
Lee, N. Z., 458
Lee, R. E., 458
Leese, C. E., 557
Lefebvre, J., 327
Lefevre, G., 529
Le Fevre, P. G., 327
Legallais, V., 448
Le Grand, Y., 249
Lehman, R. A., 418
Lehman, W. L., 129
Lehmann, H., 115, 344
Lehninger, A. L., 412
Leiby, G. M., 396, 441
Leimdorfer, A., 149, 576
Leindorfer, A., 69
Leishman, A. W. D., 398
Leiter, L., 370, 509
Leloir, L. F., 47
Le Magnen, J., 37
Lemaire, R., 69
Lemay, M. J., 538
Lemberg, R., 493
LeMessurier, D. H., 238
Lemetayer, E., 12
Lendrum, B., 415
Lenègre, J., 472
Lenggenhager, K., 478
Lennox, M., 201, 218, 219
Lennox, M. A., 199
Lennox, W. G., 199, 215
Lenz, M., 538
Leonard, S. L., 2, 21, 31, 32, 53
Leonhardi, G., 124
Leopold, I. H., 327
LePage, G. A., 10, 327, 414
Lepeschkin, E., 407
Lepow, J. P., 341
Lepp, A., 344
Lequime, J., 395
Lerique, J., 327
Lerique-Koechlin, A., 217
Lerman, J., 54
Lerman, S., 470
Leslie, S. H., 90
Lettvin, J. Y., 161, 192, 199
Leucutia, T., 532
Leuth, H. C., 346
Levander, M., 397
LeVeen, H. H., 127, 436
Levenson, S. M., 512
Levi, M., 557
Levi-Montalcini, A., 15, 16
Levin, A., 307
Levin, E., 114
Levina, L. S., 246
Levine, R., 47, 92, 420, 495
Levinson, J. E., 566
Levvy, G. A., 72
Levy, H., 30
Lévy, J., 414, 419, 420
Levy, M. N., 470
Levy, R. L., 458
Levy, R. P., 455
Lewey, F. H., 252
Lewis, D., 338
Lewis, J. H., 84
Lewis, L. A., 66, 450
Li, C. H., 51, 65, 68, 70, 71, 369, 370, 373, 374
Li, T.-W., 85, 87, 510
Liang, T., 256
Liang, T. Y., 67, 68
Libby, R. L., 379
Liberson, W. T., 199
Libert, O., 419, 420
Libet, B., 184, 185
Lichtblau, J., 124
Licklider, J. C. R., 233, 237
Liddell, E. G. T., 191
Liddle, G. W., 572, 579
Liebenow, R. R., 214, 572
Liebert, E., 327
Liebmann, A. J., 511
Liechti, A., 391
Lijon, E. W., 124
Lilienthal, J. L., 66
Lilienthal, J. L., Jr., 341
Liljestrand, A., 479
Liljestrand, G., 144, 472, 480
Lillehei, C. W., 127
Lilly, J. C., 448
Limarzi, L. R., 345, 346
Limón Lasón, R., 400
Linde, S., 109, 558
Lindeman, V. F., 251
Lindemann, E., 212
Lindgren, I., 142
Lindsay, J. R., 234
Lindskog, G. E., 469
Lindsley, D. B., 165, 168
Lineweaver, H., 11
Ling, G., 176, 307, 308
Linn, H. J., 510, 516
Linton, R. R., 91
Lipchuck, L., 448
Lipmann, F., 53, 72
Lipner, H. J., 53
Lipschutz, A., 34
Lipscomb, A., 92
Lipsett, M. B., 57
Lipton, E. L., 440
Lipton, M. A., 346
Lisco, H., 527, 531, 537
Lisi, A. G., 416
Litt, I. C., 84
Little, J. M., 128, 439, 503, 509, 567
Little, S. C., 222
Littman, A., 111

Littmann, D., 410
Livanov, M. N., 208, 210, 217
Livezey, M. M., 410
Livingston, R. B., 156, 162, 163, 208, 211, 483
Lloyd, C. W., 90
Lloyd, D. P. C., 162, 189, 193, 199
LoCascio, G., 249
Lockhart, H., 59
Lockwood, R. A., 154
Loe, P. St. J., *see* St. John-Loe, P.
Loeb, J. N., 219
Loeschcke, H. H., 479
Loew, E. R., 571
Loewe, S., 214
Lowey, A., 93
Löfgren, B. L., 179
Loftfield, R. B., 72
Logaras, G., 472, 473
Loge, J. P., 345
Loiseleur, J., 535
Lombroso, C., 117
London, I. M., 93, 335
Long, C., 414
Long, C. N. H., 67, 68, 88, 366, 368, 370, 439
Long, E. P., 514
Long, J., 410
Longcope, W. T., 476, 481
Longhurst, J. U., 284
Longmuir, N. M., 109, 558
Longsworth, L. G., 550, 551, 552, 553
Loof, J. de, *see* de Loof, J.
Loofbourow, G. N., 327
Loomis, T. A., 84, 86, 88
Loomis, W. F., 53, 72
Lopez, A. G., 390
Lopez, G. G., 337, 339, 340
Lopez, J. A., 360
LoPresti, J. L., 247
Lorch, J. I., 50
Lorente de Nó, R., 173, 174, 175, 176, 178, 179, 180, 181, 182, 183, 184, 185, 186, 188, 192, 193, 194, 549
Lorenz, E., 530, 531, 533
Lorenz, P. B., 556
Lorenzen, E., 124
Loring, H. S., 551
Lotspeich, W. D., 504, 506, 507, 509
Lou, C. H., 308, 309
Loube, S. D., 406
Louis, L. H., 68
Louwel, J., 406
Low, F. N., 256
Lowe, C. U., 124
Lowell, A., 91, 502
Lowenberg, R. J., 406
Lowenhaupt, E., 510
Lowenstein, B. E., 67, 452, 458
Lowenstein, V. E., 566
Lowry, O. H., 360
Lozinski, E., 49
Lubin, M., 401, 406
Lucas, C. C., 86, 87
Lucia, S. P., 345, 346
Lucké, B., 496
Luckiesh, M., 259
Luco, J. V., 327
Ludany, G., 152
Ludewig, S., 67, 367, 374
Luduena, F. P., 147, 572, 574, 575, 577
Ludvigh, E. J., 258
Ludwig, H., 390
Lueken, B., 482
Luetscher, J. A., 476, 481
Luisada, A. A., 390
Lukens, F. D. W., 61
Lum, R., 117
Lund, C. C., 512
Lund, M., 450
Lundbaek, K., 103, 122
Lundberg, A., 187
Lundin, G., 298, 412, 420
Lundquist, F., 378
Lundy, J. S., 575, 579
Luneberg, R. K., 258, 260
Lups, S., 92
Lupton, A. M., 484
Lura, H. E., 105
Lurie, M. H., 234
Lusk, G., 58
Lutz, H., 7
Lwoff, A., 484
Lynch, J., 327
Lynn, W. G., 6
Lyon, R. A., 406
Lyons, R. H., 458, 566, 567, 568, 569
Lyubimova, M. N., 317

M

Maaløe, O., 122
McArthur, J. W., 61
McCall, W., Jr., 406
McCance, R. A., 498
McCarter, R. H., 207
McCarthy, H. M., 456
McCarthy, M. D., 440, 475
McCawley, E. L., 212
McClendon, J. F., 55
McClure, J. A., 256
McConnell, K. P., 29
McCord, C. P., 86
McCord, F., 258
MacCorquodale, K., 256
McCoy, R. H., 378
McCrady, E. J., 233
McCullagh, E. P., 38, 59, 66
McCulloch, W. S., 155, 161, 162, 164, 165, 167, 199, 204, 208, 211, 260, 278
McCune, D. J., 61
McCutcheon, F. H., 13
McDonald, D. F., 72
McDonald, P. R., 250
McDonald, R. K., 63
MacDonald, R. M., 104, 118
McDowall, R. J. S., 149, 417, 456
MacFarlan, D., 242
McGinnies, E., 280, 292
McGinty, D. A., 59
McGowan, J. M., 578
Machella, T. E., 88
McIntosh, B. C., 390
McIntyre, A. K., 189, 193
McIntyre, A. R., 201, 215, 317
Mack, H. C., 27
Mack, I., 395, 469
McKay, E. A., 456
MacKay, E. M., 128, 510
Mackay, I. F. S., 116, 446
MacKay, L. L., 510
Mackenzie, C. G., 495
Mackenzie, E. R., 406
McKittrick, D. S., 495
Maclagan, N. F., 83
McLain, P. L., 460
McLardy, T., 162
MacLeod, J., 32
McMahon, R. A., 141
McManus, M. J., 446
McMaster, P. D., 356
McMichael, J., 400, 401, 402, 472
McNamara, B., 456
McNamara, H., 498, 505
McNamara, W. L., 73
MacNichol, E. F., 251

McShan, W. H., 6, 23, 38, 51, 52
McSwiney, B. A., 125, 144
Madden, R. A., 124
Maddock, S. 117
Maddock, W. D., 571
Maddock, W. O., 38
Madison, C. R., 379
Maegraith, B. G., 515
Maes, J. P., 147, 450
Magee, J. L., 321
Magitot, A., 246
Magoun, H. W., 164, 165, 167, 168, 199, 208, 211
Mahaim, I., 388, 390
Maher, E. B., 293
Maier, N. R. F., 284
Mainini, C. G., *see* Galli-Mainini, C.
Maione, M., 256
Maizels, M., 555, 557
Majnarich, J. J., 340, 348
Majumder, D. N., 345
Malamud, W., 222
Malcolm, J. L., 189, 192, 298
Malinow, M. R., 152
Mallarmé, J., 346
Malmejac, G., 153
Malméjac, J., 148, 370, 469
Malmo, R. B., 258
Malmros, R., 217
Maloney, J., 578
Malton, S. D., 567, 571
Maluf, N. S. R., 119
Man, E. B., 53, 59, 60
Mandel, P., 6
Mandelbaum, J., 256
Mandernach, D. M., 60
Manery, F. J., 556
Manges, W. E., 107
Mangun, G. H., 327, 411
Mankin, H., 91, 502
Mankin, J., 245
Mann, F. C., 91, 118
Mann, F. D., 83
Mann, I., 256
Manning, I. H., 346
Manry, C. H., 457
Mansell, H. E., 518
Marble, A., 50
Marchal, J., 469
Marchal, M., 460, 474
Marchetti, A. A., 38
Marcus, H., 63
Maresh, G. J., 421
Margaria, R., 206
Mark, D. D., 202
Markee, J. E., 33, 35, 36, 154, 327
Marks, E. K., 371, 533
Marks, J. L., 390
Marks, M., 162
Maroger, M., 470
Marquardt, P., 69
Marrazzi, A. S., 148, 149, 457, 569, 572
Marrazzi, R. N., 148, 149, 457, 569, 572
Marrian, G. F., 27
Marsan, C. A., 221
Marsh, B. S., 174
Marsh, J. B., 49, 50
Marshall, C., 221, 453
Martin, A. W., 327, 484
Martin, C. E., 38
Martin, C. J., 495
Martin, G. J., 58, 327, 341
Martin, H., 84
Martin, J., 162
Martin, L. C., 255, 259
Martin, N. H., 83, 93
Martin, R. A., 86
Martin, S. F., 258
Martinez, J. S., *see* Santos-Martinez, J.
Martini, E., 206, 207
Martini, V., 122
Marvel, C. S., 511
Marvin, H. N., 25
Marx, M. H., 293
Marx, W., 59
Marzoni, F. A., 568
Marzorati, A., 206, 207
Marzulli, F. N., 480
Mascarenhas, A., 410
Masland, R. L., 195
Mason, H. L., 66, 68, 370, 374
Mason, J. W., 111
Mason, M. F., 85, 87, 92
Masson, G., 123
Massopust, L. C., 327
Master, A. M., 407
Masters, R. E., 335
Mateer, J. G., 83
Mathieu, M., 551
Mathur, P. D., 118
Matlock, W. P., 392, 393, 395, 414
Matoltsy, A. G., 312
Matteucci, P., 246, 248
Matthews, B. H. C., 189, 200
Matthews, L. H., 26
Mattioli, M., 388
Mattocks, A. M., 341
Mauer, I., 213, 215
Maun, M. E., 362
Maurice, P., 472
Maxwell, L. J., 245
Mazars, G., 208
Mazur, A., 90
May, C. D., 124
May, J. R., 124
Mayer, M. M., 374
Mayfield, F., 327
Mead, S., 327, 482
Means, J. H., 538
Meda, E., 478, 479
Mederos, L. O., 305
Medica, G., 484
Medinets, H. E., 570
Meeham, H., 473
Meehan, J., 439
Meek, W. J., 152
Mehl, J. W., 57, 85
Meier, K. G., *see* Gollwitzer-Meier, K.
Meier, R., 477, 484
Meijer, F. G. D., 92
Meinberg, W. H., 249
Meinenberg, L. J., 84
Meitina, R. A., 317
Melampy, R. M., 344
Melin, K. A., 216
Mello, M. I., 35
Mendel, B., 418
Mendes, E. G., 2
Méndez, R., 413, 419
Meneely, G. R., 396, 441
Menkin, M. F., 21
Menten, M. L., 495, 511
Mentha, J. W., 341
Menzies, J. T., 494
Mercier, E., 36
Mercier, P., 360
Merendino, K. A., 111, 129
Merrill, A. J., 401, 503
Merrill, P., 59
Merten, R., 360
Mertens, E., 376, 378
Meserve, E., 59
Metchnikoff, E., 378
Metcoff, J., 83, 344
Metheny, D., 440
Mettler, F. A., 162, 165, 166, 167
Metz, B., 151
Meyer, A., 162
Meyer, A. E., 416
Meyer, E. Z., 8
Meyer, J., 360
Meyer, J. de, *see* de Meyer, J.

Meyer, K., 129
Meyer, K. A., 111, 567
Meyer, K. H., 561
Meyer, L. M., 338, 341
Meyer, P., 410
Meyer, R. K., 6, 23, 38, 51, 52
Meyer, S., 415
Meyerhof, O., 69, 298, 311, 314, 323, 325
Meyers, J. W., 538
Meyers, W., 538
Miall, M., 315, 323
Micetich, A., 571
Michaelis, L., 120, 344
Michaels, G. D., 85
Michelsen, J. J., 327
Michelsen, O., 493
Michie, C. R., 390
Mider, G. B., 362
Mignot, J., 56
Mikkelsen, W. P., 372
Milanes, F., 337, 339, 340
Milder, B., 249
Miles, M., 327
Miles, P. W., 257
Milhorat, A. T., 327
Miller, A. A., 84
Miller, A. T., Jr., 94, 435
Miller, B. S., 457, 573
Miller, C., 533
Miller, D., 208
Miller, D. C., 67
Miller, E. W., 162
Miller, F. R., 484
Miller, J. L. E., 307
Miller, L. C., 574, 575, 577, 579
Miller, L. L., 88
Miller, M., 410
Miller, O. B., 110
Miller, R. A., 477, 484
Miller, W. H., 60
Miller, W. W., 72
Miller, Z. B., 360
Milliez, P., 470
Millikan, G. A., 484
Millis, J., 120
Mills, I. H., 11, 12, 36
Milne, J., 373
Minder, W., 528
Minet, J., 471
Minz, B., 150, 418
Miquel, O., 418
Mirone, L., 30
Mirsky, A. E., 2, 321, 356
Mirsky, I. A., 46, 114
Misiak, H., 255
Mispireta, D., 410
Mitchell, J. S., 529
Mitolo, M., 470, 478
Mittleman, N., 47
Mixer, H. W., 94, 368
Moe, G. K., 458, 565, 566, 567, 568, 569, 570, 571, 573
Moehlig, R. C., 66, 73
Moguel, R. B., *see* Barroso-Moguel, R.
Mokotoff, R., 509
Molano, P. A., 446
Molina, A. F. de, *see* de Molina, A. F.
Molle, W. E., 110
Mommaerts, W. F. H. M., 314, 315, 323, 411
Monaco, A. R., 85
Monahan, E. P., 214
Mondolfo, H., 374, 376
Mongar, J. L., 323
Monke, J. V., 517, 518
Monnier, A. M., 180, 183, 184
Monnier, M., 209, 252
Monod, J., 3, 484
Monroy, A., 1
Montalcini, A. L., *see* Levi-Montalcini, A.
Montalenti, G., 1
Monteil, R., 511
Montgomery, G. E., 477, 484
Montgomery, L. H., 448
Montgomery, M. L., 87
Montgomery, T. L., 28
Moog, F., 9
Moolten, S. E., 360
Moon, P., 251, 259
Moore, C., 459
Moore, C. R., 23
Moore, C. V., 121, 335, 344
Moore, D. H., 374
Moore, E., 444, 556
Moore, J. A., 4
Moore, J. C., 435, 436
Moore, M. C., 531, 532, 534
Moore, P. R., 344
Morales, M., 325
Moran, C. F., 580
Morehead, R. P., 509, 511
Morehouse, M. G., 85
Morel, J., 149
Moreton, J. R., 454
Morgan, A. F., 58
Morgan, C. P., 235
Morgan, C. T., 288
Morgan, M. W., Jr., 248
Morgan, K. Z., 527
Morgans, M. E., 339
Morgulis, S., 314
Moriarty, J. D., 222
Morice, J., 218
Morrione, T. G., 86
Morris, R. E., Jr., 143
Morrison, J. L., 568
Morrison, S., 107, 130
Morrissey, M. J., 475, 484
Morse, M., 436
Mortarotti, T. G., 458
Mortensen, O. A., 327
Morton, G. M., 112
Morton, R. A., 250
Moruzzi, G., 220, 481
Moseley, H. R., 6
Moses, C., 86
Mosovich, A., 217, 218, 222
Moss, E., 273
Moss, J., 341
Moss, W. G., 566, 570
Mossberger, J. I., 154
Moszkowska, A., 56
Motley, H. L., 400, 401, 410, 471, 472, 474
Mount, L. E., 62
Mountcastle, V. B., 162
Movitt, E. R., 83
Mowat, J. H., 341
Mowbray, R., 60
Moya, F., 69
Mozer, J. J., 406
Mrazek, R. G., 313
Mudge, G. H., 506
Mueller, A. J., 85
Mueller, C. G., 255
Mukherjee, A. B., 390
Mukherjee, S., 124
Mulder, A. G., 514
Mulder, D. W., 221
Müller, A., 476
Müller, H. R., 483
Mullins, L. J., 401
Munks, B., 8
Munnell, E. W., 92, 442
Muñoz, E., 327
Munro, F. L., 89, 441
Munro, M. P., 89, 441
Muntz, J. A., 528, 534, 536
Murison, P. J., 573
Muro, P. de, *see* de Muro, P.
Murphree, R. L., 23
Murphy, F., 222
Murphy, J. B., 368, 376

Murphy, J. P., 154, 217
Murphy, Q., 152
Murphy, R. C., 415, 441, 457
Murray, C. W., 11
Murray, H. C., 340
Murray, M. R., 140
Murray, R., 531
Murray, V., 444
Murtaugh, J. J., 511
Mushett, C. W., 128, 340, 362
Mussio-Fournier, J. C., 37
Muylder, C. de, *see* de Muylder, C.
Myers, J. D., 92, 442
Myers, V. C., 327, 411
Mylon, E., 449, 450, 455

N

Nase, G. W., 12, 13
Nachmansohn, D., 184, 185, 186, 213, 309, 417, 418, 553
Naeslund, J., 555, 560
Nageotte, J., 245
Nahum, L. H., 408
Narahara, H. T., 2
Nash, V. L., 456, 457
Nasio, J., 129
Nathanson, N. H., 396
Naumann, H. N., 93
Nauta, W. J. H., 155, 247
Neal, W. B., Jr., 129
Necheles, H., 104, 107, 117, 130
Needham, D. M., 15, 315, 323, 360
Needham, J., 315, 323
Neefe, J. R., 83, 92
Neff, W. D., 235, 236, 237, 240
Neil, E., 151, 459
Neira, J., 410
Neligh, R. B., 458, 566, 567, 568, 569
Nelson, J. F., 47, 48
Nelson, M. M., 30
Nelson, R. A., 64
Nelson, W. O., 34
Nelson, W. W., 368, 369, 372
Nennaux, L., 32
Nesbit, R. M., 567
Nestoresco, B., 372, 374
Netsky, M. G., 221
Neu, L., 528
Neu, V., 528
Neuberger, A., 88
Neverre, G., 153
Neville, J. F., Jr., 397
Newell, G. W., 214
Newhall, A., 346
Newhouse, M. L., 85
Newman, E., 503
Newman, E. A., 89
Newman, E. V., 505
Newton, W. H., 28
Nezamis, J. E., 63, 64, 65
Nichol, C. A., 340
Nicholas, J. S., 9, 10
Nicholas, S., 86
Nickerson, J. L., 398, 458
Nickerson, M., 569, 570, 571
Nickson, M., 535
Nicol, L., 12
Nicolau, C., 372, 374
Nielsen, A. T., 31
Nielson, J. M., 260
Niini, R., 253
Nimeh, W., 107
Nimmo-Smith, R. H., 473
Nims, L. F., 164, 479
Niu, M. C., 15
Nixon, D. L., 201
Nixon, W. L., 52
Nizet, A., 436
Nó, R. L. de, *see* Lorente de Nó, R.
Noback, C. R., 398, 459
Noble, R. P., 397
Noell, W. K., 476, 484
Nolasco, J. B., 143, 399, 482
Nomaguchi, G. M., 569, 570, 571
Noonan, T. R., 335
Noran, H. H., 162
Norris, E. R., 340, 348
Norris, L. C., 5, 341
Northrup, D. W., 107, 118, 120
Novikoff, A. B., 8, 10, 413
Nudell, G., 475
Nulsen, F. E., 164, 165
Nutt, M. E., 497
Nyffeler, M., 391
Nylin, G., 395, 396, 397, 402, 437, 555, 560

O

Oberhelman, H. A., Jr., 129
Oberholzer, R. J. H., 482
Obrador, S., 162
Obreschkow, G., 479
O'Brien, B., 253
O'Brien, J. M., 249
O'Brien, J. R. P., 90, 477
Obrig, T. E., 245
Öbrink, K. J., 109, 114, 555, 558
Ochoa, S., 298
O'Connor, A. D., 249
O'Day, K., 247
Oddone, M. V. G., *see* Gonzalez-Oddone, M. V.
Odel, H. M., 119, 120
Odell, L. D., 72
Odor, D. L., 26
Odoriz, J. B., 217
Oesper, P., 314
Oester, Y. T., 327
Ofner, P., 574, 575, 576
Ogden, E., 442, 444, 449, 571
Ogle, B. C., 503, 567
Oglialoro, C. M., 476
Ogston, A. G., 25
Ogur, M., 413
Öhman, L. O., 1
O'Leary, J. L., 161, 222
Oleson, J. J., 341
Olitsky, P. K., 85
Olivecrona, H., 142
Oliver, J. V., 130
Olivieri, E., 37
Olivo, O. M., 409
Ollivier, H., 222
Olmsted, J. M. D., 248
Olsen, N. S., 63
Omachi, A., 308
O'Neal, K. C., 447
O'Neill, J. C., 247
O'Neill, S. L., 21, 389
Oogle, B. C., 128
Opdyke, D. F., 92, 399, 406, 407
Oppenheimer, G. D., 119
Oppenheimer, J. M., 7
Oppenheimer, M. J., 89, 118, 390, 410, 567
Ordway, N. K., 440, 477, 517
Ornitz, E. M., 471
Ornitz, E. M., Jr., 91, 448
Orozco, F. V., *see* Velez Orozco, F.
Ørskov, S. L., 555, 556, 557
Orth, O. S., 214, 572
Osborne, S. L., 327
O'Shaughnessy, L., 518
Oshlag, A. M., 574, 579
Oster, G., 312, 315, 316

Oster, J., 452
Oster, R. H., 69
Osterberg, A. E., 117, 126, 495
Osterheld, R. G., 216, 218
Osterhout, W. J. V., 556
O'Sullivan, H. J. L., 211, 215, 219
Otis, A. B., 401, 442, 470, 473, 474, 475, 478, 479, 484
Ottesen, J., 358, 359
Overbeek, J. T. G., 553
Overbey, D. T., 435
Overman, R. R., 437, 555, 557
Owren, P. A., 346, 441

P

Pacalin, G., 248
Pace, N., 477
Pacella, B. L., 200, 222
Pack, G. T., 573
Paegel, B. L., 338
Pagé, E., 344
Page, E. W., 579
Page, I. H., 92, 449, 450, 452, 453, 456, 458, 494, 505, 513, 518, 566, 567, 568
Pai, M. L., 502
Paillas, J., 470
Paillas, J. E., 218
Painter, E. E., 437, 531, 534
Pallares, D. S., *see* Sodi Pallares, D.
Pallares, E. S., *see* Sodi Pallares, E.
Palm, E., 246, 555, 559
Palmer, B., 94
Palmer, E. D., 110
Palmer, H., 221
Palmer, W. L., 114
Palmer, W. W., 515
Pankratz, D. S., 514
Pannier, R., 142, 389, 484
Pantaleon, J., 116
Panzardi, D., 246, 248
Panzer, B. I., 442
Paolino, W., 115
Papanicolaou, G. N., 38
Papez, J. W., 164
Pappenheimer, J. R., 484
Papper, E. M., 475
Parets, A. D., 454
Parfitt, N. D., 218
Parin, V. V., 152, 459, 472
Parker, F., Jr., 35
Parker, H. M., 527
Parkes, A. S., 33, 54
Parkhurst, C., 308
Parkins, W. M., 440
Parks, A. E., 27
Parpart, A. K., 556
Parpart, E., 556
Parr, G., 199, 202, 204, 216
Parrish, D. B., 13
Parry, T. M., 478
Parsons, D. S., 515
Partridge, S. M., 13
Pasargiklian, M., 478
Pascal, J. I., 249
Paschkis, K. E., 30, 31
Pastor, S., 217
Patch, E. A., 508
Patek, A. J., Jr., 83, 85, 91, 93, 502
Pathman, J. H., 201, 203
Patras, M. C., 72
Patt, H. M., 367, 529, 535, 536
Patterson, J. F., 126
Patterson, J. M., 87
Patterson, L., Jr., 256
Patterson, M. B., 92
Patterson, T. L., 107, 114
Pattle, R. E., 169
Patton, M. F., 421
Patton, R. A., 285, 286, 289
Paul, W. D., 114, 128
Pauls, F., 114, 128
Paulsen, E. C., 343
Peacock, W., 59
Peacock, W. C., 121, 440
Pearce, R. H., 53
Pearlman, N., 530, 533
Pearlman, W. H., 31
Pearse, R. W. B., 259
Pearson, R., 415
Peckham, B. M., 24
Peden, J. K., 207
Pedersen-Bjergaard, K., 31
Peeney, A. L. P., 123
Peet, M. M., 566
Pellegrino, E., 93
Pellmont, B., 477, 484
Pellon, R., 409
Pelou, A., 327
Peñaranda, J. M., 34
Pencharz, R. I., 33
Pendergrass, E. P., 533
Penfield, W., 161, 166, 167
Penfold, J. B., 512
Pehos, J. C., 122
Pennel, R. B., 519
Pennes, H. H., 217, 218
Penneys, R., 477
Pentz, E. I., 495
Pentzik, A. S., 216
Peralta, B., 413, 415, 568, 573
Percival, W. L., 61
Perdrup, A., 327
Pereira, J., Jr., 305
Pereira, S. A., 565
Pereiras, R., 390
Perera, G. A., 90, 451, 455
Perez Simon, A., 391
Perianes, I., 389
Perisutti, G., 46
Perkins, J. F., 298, 327
Perkins, R. F., 217
Perlman, P. L., 2, 21, 31, 32, 53
Perlmutter, M., 48
Perlstein, D., 511
Perlstein, M. A., 215
Perry, S. V., 313, 314, 315, 316, 317, 322
Perry, T. T., 355
Perryman, R., 533
Persike, E. C., 58
Personeus, G., 448
Pertzoff, V. A., 447
Peterfalvi, M., 304
Petering, H. G., 340
Peters, H. N., 272
Peters, J. H., 494
Peters, J. P., 53, 59, 510, 555, 556, 557
Petersen, A., 317
Petersen, W. E., 29
Peterson, E., 368
Peterson, J. H., 249
Peterson, J. M., 477
Peterson, L. W., 439
Petitpas, T., 551
Petralia, S., 409
Pettinga, F. L., 153
Peyser, E., 479
Peyton, W. T., 162
Pezeu, M. H., 313
Pfeiffer, C. A., 30, 90
Pfeiffer, C. C., 574, 575, 579
Pfister, A., 249
Phatak, N. M., 578
Phemister, D. B., 91
Philippot, E., 484
Philips, F. S., 376, 379
Phillips, P. H., 12, 30

Phillips, R. A., 439, 494, 500, 501, 508, 509, 512, 513, 516, 519
Phillips, R. W., 36
Phillipson, A. T., 126
Philpot, J. S. L., 25
Phipps, P. J., 355, 473
Pichot, P., 219
Pick, E. P., 90
Pickford, R. W., 258
Piedelievre, R., 388
Pieron, H., 253, 256
Pietri, R., 327
Pigeaud, H., 27
Pil'don, Z. A., 115
Pilgrim, F. J., 289
Pillet, J., 360
Pillion, E. L., 444
Pimenta, A. M., 217
Pincus, G., 222, 368, 370, 371
Pincus, I. J., 116
Piney, J., 484
Pinkerton, H., 11
Pinkston, J. O., 146
Pinotti, O., 479
Piquet, J., 418
Pircher, L., 476
Pirenne, M. H., 253, 254
Pisanty, J., 415
Pisha, B., 109
Pi Suner, A., 139
Pitt Rivers, R., 54
Pitts, R. F., 504, 507, 508, 509
Pitts, W., 204, 260, 278
Pizzolato, P., 345
Plagge, J. C., 365
Planques, J., 221
Platt, J. R., 253
Plessinger, V. I., 410
Plicque, J., 256, 257
Plotka, C., 150
Plum, C. M., 115, 341, 342, 343, 345, 347
Podore, E. J., 114
Pohlman, M. E., 232
Poli, E., 557
Poliakov, K. L., 208, 210
Policard, A., 469, 470, 473
Polis, B. D., 314
Pollack, H., 63
Pollack, M. R., 84
Pollard, H. M., 111
Polley, J. R., 451
Pollister, A. W., 356
Pollock, L. J., 327
Polvogt, L. M., 236
Polzer, K., 391
Pomeroy, W. B., 38
Pommerenke, W. T., 32
Ponder, E., 555, 556
Ponomarev, G. A., 124
Ponz, F., 49, 121
Poo, L. J., 497
Popják, G., 8, 28
Popkin, R. J., 574, 576, 577, 579, 580
Poppen, J. L., 452
Popper, H. L., 117
Porter, L. M., 533
Porter, P. B., 280, 281
Porter, R. R., 13, 344
Porteus, S. D., 272
Posey, E. L., 111
Post, L. T., 249
Posternak, J. M., 194
Potter, V. R., 8, 10, 412, 413
Potts, W. J., 389
Pou de Santiago, A., 35
Poulson, A. D., *see* Dubois-Poulson, A.
Power, M. H., 61, 66, 68, 117, 370, 374
Powers, E. L., Jr., 536
Prado, J. L., 69, 451
Praetorius, E., 358
Pratt, T. D., 117
Prentice, W. C. H., 259
Pressman, D., 511
Preston, F. W., 114
Preston, S. N., 477
Prestrud, M. C., 63, 64, 65, 68, 71
Price, D., 14, 26
Price, P. B., 128
Price, W. H., 45
Prichard, M. N. L., 451, 496
Pringle, A., 341
Prinzmetal, M., 91, 405, 407, 448, 471
Pritchard, J. A., 340
Pritchard, J. J., 25, 51
Pritchard, W. H., 416
Proctor, D. F., 470
Proctor, L. D., 215, 218, 219
Proger, S., 413
Prokofyeva-Belgovskaya, A. A., 3
Prosser, C. L., 531, 532, 534
Prosser, M., 62
Prudden, J. F., 129
Pruitt, R. P., 408
Prunty, F. T. G., 68, 370, 374
Pruss, O. C. H., *see* Hansen-Pruss, O. C.
Puddu, V., 409
Puech, P., 217, 218, 222
Pugh, E. J., 62
Pugsley, L. I., 30
Pullman, T. N., 573
Pupo, P. P., 217
Purslow, E. T., 258
Purves, H. D., 54, 60
Putnam, T. J., 217

Q

Quadfasel, F. A., 221
Quelch, P. E., 477
Quick, A. J., 441
Quigley, J. P., 106, 107
Quimby, E. H., 61, 470
Quimby, F. H., 361, 366
Quinquaud, A., 484

R

Raab, D. H., 238
Raab, W., 147, 417, 456
Rabinovitch, J., 27
Rabinovitch, M., 105
Rachmilewitz, M., 346
Radde, C. A., 248
Radice, J. C., 124
Radnot, M., 246
Ragan, C., 528
Rahn, H., 401, 442, 473, 474, 475, 478, 479, 484
Rakoff, A. E., 30, 31, 34
Rall, D. P., 571
Ralli, E. P., 63, 90
Ralston, H. J., 298, 302, 306, 458
Ralston, W., 396, 441
Ramos, J. G., *see* García Ramos, J.
Ramsay, W. N. M., 477
Ramsey, R. W., 298, 299, 300, 302, 304, 305, 321, 323, 325, 395
Ramsey, V. W., 327
Rand, G., 258
Randall, L. O., 69
Randles, F. S., 415
Rankin, V. M., 458, 571
Ransmeier, R. E., 185, 195
Ranstrom, S., 167
Ranzi, S., 7

Rao, R., 87
Rapela, C., 503
Raper, J. R., 528, 534, 535
Raper, L. A., 152, 472
Rappaport, M. B., 390
Rapport, D., 71
Rasmussen, T., 161, 221
Ratcliffe, A. H., 567
Rather, L. J., 90, 517, 519
Raulli, M. L., 484
Ravdin, I. S., 89
Ravin, A., 407
Rawles, M. E., 15
Rawson, R. W., 59, 61
Ray, B. S., 141
Ray, G. K., 122
Ray, T., 567
Raymond, W. B., 128
Raynaud, A., 14, 26
Raynaud, J., 26, 37
Read, J., 530
Reardon, M. J., 568
Reaves, D. P., 475
Reaves, J. U., 513
Redish, J., 509
Redlich, F. C., 221
Redondo, H. P., 478
Redwood, C. R. M., 151, 459
Reed, B. P., 33
Reed, C. I., 33, 313
Reed, E. A., 482
Reed, F. B., 120
Reed, H. L., 155
Reed, J. A., 110
Reed, R., 312, 315
Reenpää, Y., 253, 254
Rees, D. S., 46
Reese, J. W., 72
Regan, M., 338, 340
Rehm, W. S., 109, 558
Reichert, F. L., 56, 87
Reichsman, F., 152
Reid, C., 63, 64
Reid, C. H., 245
Reid, G., 70
Reid, M. E., 119
Reid, R., 512
Reifenstein, E. C., Jr., 67
Reimert, L. J., 255
Reinhard, J. J., 92, 568
Reinhardt, W. O., 88, 362, 369, 372, 373
Reinhold, J. G., 83, 92
Reiser, M. F., 566, 567
Reiss, B. F., 292
Reiss, M., 46, 67, 68, 70, 370
Reiss, R. A., 399, 400
Reissig, M., 165
Reitman, F., 162
Rekers, P. E., 533
Remington, D. W., 397
Remington, J. W., 397, 398, 399, 459
Rémond, A., 201, 218, 221
Rémy, M., 199, 202
Rennick, B. R., 458, 566, 567, 568, 569, 571
Renshaw, B., 192
Řeřábek, E., 60
Řeřábek, J., 60
Reubi, F. C., 496
Revesz, J., 459
Reynals, F. D., *see* Duran-Reynals, F.
Reynolds, M., 402
Reynolds, S. R. M., 27, 28, 447, 448
Rezenfeld, I. H., 327
Rhines, R., 168
Rhoads, J., 377, 379
Rhoads, P. S., 510
Ricamo, R., 409
Rice, H. V., 559
Rich, A. R., 88, 89
Richards, D. W., 474
Richards, D. W., Jr., 397, 400, 404, 410
Richardson, A. P., 457, 573
Richardson, E., 450
Richardson, G. S., 477, 484
Richardson, J. S., 85
Richins, C. A., 140, 141, 142, 248, 460
Richter, C. P., 104, 141, 242
Richter, K., 24
Rickards, E. E., 457
Riddell, C., 59
Ridout, J. H., 87
Riegel, C., 85
Riesen, A. H., 255
Riesser, O., 48
Riggs, L. A., 252
Rigler, L. G., 94
Rijlant, P., 394, 482
Riker, W. W., 84
Riley, E. F., 531
Riley, G. M., 35
Riley, R. L., 397, 472
Rimington, C., 60, 93, 339
Ring, G. C., 390
Rinkel, M., 156, 208
Ris, H., 356
Risley, E. A., 128
Risman, G. C., 27
Ritchie, G., 572
Ritchie, J. M., 298, 301
Ritchie, W. S., 344
Rittenberg, D., 93, 335
Rittenberg, R., 89
Rittler, M. C., 258
Ritz, N. D., 341
Rivero Carvallo, J., 416
Rivers, R. P., *see* Pitt Rivers, R.
Robb, J. S., 387, 388, 408, 409
Robbie, W. A., 10
Robbins, B. H., 518
Robbins, E. B., 576, 577, 580
Robbins, S. L., 35
Robblee, A. R., 340
Roberts, J. T., 389, 406
Roberts, S., 30, 90, 357, 358, 377, 379
Robertson, C. R., 111, 129
Robertson, G. G., 21, 389
Robertson, J. S., 364
Robertson, R. L., 443, 444 458
Robin, E. D., 368, 371, 557
Robinson, C. O., 7
Robinson, J., 483
Robinson, L. J., 216, 218
Robison, P., 495
Robles, G. J., 414
Roblin, R. O., Jr., 60
Robson, J. S., 90
Rocha e Silva, M., 441
Rochon-Duvigneaud, A., 245
Rock, J., 21, 36
Rockey, E. E., 437
Rockwell, F. V., 222
Rockwell, P., 397
Rodbard, S., 69, 399, 441, 458, 459, 472, 473, 478, 570
Rodney, G., 341
Rodriguez, R., 69
Roemmelt, J. C., 507, 509
Rogers, C. A., 88
Rogers, J. W., 119
Rogers, L. L., 340
Rogers, W. N., 86
Rolf, D., 70, 399, 416, 497, 504
Romano, J., 214, 216
Romijn, C., 484
Roos, A., 397
Root, H. F., 50

Root, M. A., 567
Root, W. S., 346, 399, 402, 437, 440
Rose, A., 254
Rose, C. S., 88, 90
Rose, F. L., 124
Rose, H. W., 253
Roseman, E., 217, 218
Rosenak, S., 119
Rosenbaum, F. F., 410
Rosenbaum, H., 192
Rosenberg, I. M., 478
Rosenberg, L., 114
Rosenblueth, A., 148, 205, 278, 392, 393, 395, 410, 417
Rosenfeld, F. M., 416
Rosenfeld, L., 355, 363
Rosenkrantz, J. A., 453
Rosenthal, F., 28
Rosenzweig, M. J., 238
Rosin, A., 86, 346
Rosinov, V. S., 217
Ross, G., 509
Ross, G. R., 515
Ross, J. B., 400
Ross, J. F., 338
Ross, R. T., 559
Ross, S., 255
Rossien, A. X., 111
Rossier, P. H., 410, 478
Rossiter, R. J., 115
Rostand, J., 7
Roth, C. B., 5
Roth, G. M., 444, 458
Rothenberg, M. A., 181, 184, 186, 213, 309, 555, 559
Rothlin, E., 572
Rothman, T., 216
Rothschild, Lord, 561
Rottenberg, W., 552
Roubicek, J., 201, 208
Roussel, F., 255
Routh, J. I., 114, 128
Routier, D., 410
Routier, R., 410
Rovenstine, E. A., 574, 576, 578, 579
Rowinski, P., 470
Rowlands, I. W., 23
Roy, A., 71
Royer, P., 480
Rozan, A., 249
Rubarth, S., 87
Rubenstein, H. S., 222
Ruch, T. C., 163, 201
Rudall, K. M., 312
Rudd, J. L., 327
Ruedi, L., 235
Rueff, C. G., *see* Grezes-Rueff, C.
Rueff, F. A. G., *see* Grezes-Rueff, F. A.
Ruegamer, W. R., 340
Ruehrwein, R. A., 495
Ruf, C., 235
Rumsey, C. C., 475
Rune Frisk, A., *see* Frisk, A. R.
Rushmer, R. F., 447
Ruskin, A., 397, 441
Russell, D. S., 390
Russell, J. A., 71, 366
Russell, R. W., 290
Russo, H. F., 508
Russo, P. E., 94
Ryan, J. J., 222
Rybak, B., 3
Rydin, H., 151
Ryland, C. R., 327
Rynearson, E. H., 68, 370, 374

S

Sabin, F. R., 378
Sabin, S. S., 405
Saccomanno, G., 142
Sacher, G. A., 530, 533, 536, 537
Sachs, E., 483
Sacks, J., 527
Sacks, J. G., 272
Sadhu, D. P., 57, 58, 60, 418
Sadowsky, A., 28
Safford, H., 154
Sager, O., 217
Sagerson, R. P., 473
St. John-Loe, P., 203
Sakharova, D. S., 125
Sala, O., 250
Salah, M. K., 250
Salis, H., 340
Salisbury, G. W., 32, 36
Salomon, K., 6
Salter, W. T., 90, 356, 420, 421
Saltzman, A., 83
Saltzman, A. H., 68
Saltzstein, H. C., 114, 128, 130
Samaan, A., 481
Sammons, H. G., 123
Sampson, J. J., 448
Sanders, J. H., 33
Sanders, T. E., 249
Sandifer, P. H., 327
Sandow, A., 298, 301, 302, 305, 306, 309, 310, 323, 325
Sands, I. J., 218
Sandweiss, D. J., 114, 128, 130
Sanger, F., 13, 344
Sano, M. E., 28
Santos-Martinez, J., 575
Sapirstein, L. A., 449
Sarenko, P. F., 56
Sargent, F., 338
Saris, D., 482
Sarnoff, S. J., 458, 570, 571
Sartorius, O. W., 507, 509
Sass-Kortsák, A., 479
Saunders, J. A., 483
Saunders, P. R., 416
Savard, K., 69
Sawitsky, A., 341
Sawyer, C. H., 33, 35, 36, 84, 154
Sayers, G., 67, 68, 366
Sayers, M. A., 67, 68, 366
Scanlon, M. H., 344
Scantlebury, R. E., 107
Scarff, R. W., 512
Scatchard, G., 552
Schachter, M., 222
Schaefer, A. E., 344
Schaefer, H., 298, 301
Schaeffer, G., 149
Schafer, E. P. S., *see* Sharpey-Schafer, E. P.
Schafer, P. W., 91
Schallek, W., 194, 569
Schapira, G., 327
Schaposnik, F., 449
Schechtman, A. M., 11, 12, 13
Scheer, B. T., 2
Scheinberg, P., 443, 444
Scheiner, H., 304, 308, 309, 555, 557
Scheinfinkel, N., 309
Schemm, F. R., 90
Schiess, W. A., 507
Schiff, L., 83, 110
Schiffer, F., 65
Schilling, J. A., 122
Schlaer, S., 254, 255
Schlapp, W., 399
Schlesinger, B., 217
Schlesinger, E. B., 217, 218
Schlichter, J. G., 393, 396, 441

Schlosberg, H., 288
Schlutz, F. W., 436
Schmerl, E., 246
Schmid, F., 31
Schmidt, C. F., 471, 536
Schmidt, C. L. A., 495
Schmidt, G., 9
Schmidt, H. L., Jr., 245
Schmidt, I., 253
Schmiterlöw, C. G., 146, 308
Schmitt, F. O., 298, 311, 312, 319
Schneider, J., 481
Schneider, R. W., 59
Schober, H., 249, 252
Schoepfle, G. M., 193, 298, 301, 302, 305, 323
Scholander, P. F., 477, 484
Scholz, R. O., 246
Schønheyder, F., 89
Schreiner, L. H., 165, 168
Schrek, R., 364, 367
Schroeder, H. A., 450, 455, 496
Schroeder, M. S., 27
Schueler, F. W., 419
Schulman, J. H., 551
Schulman, M. P., 72
Schultz, J., 3
Schumacker, H. B., Jr., 406, 445
Schwartz, F., 252
Schwartz, L. L., 405
Schwartz, S., 533
Schwartz, S. O., 338, 346
Schwartz, W. B., 390
Schwartzman, G., 437
Schwarz, G. S., 390
Schwarz, K., 88
Schweigert, B. S., 7, 493
Schweinburg, F., 126
Schweitzer, A., 151, 459
Schweizer, W., 60
Schwob, A., 414, 419, 420
Sciarini, L. J., 420
Scobee, R. G., 248
Scolnik, R., 249
Scott, C. C., 94, 484, 576, 577, 580
Scott, E. M., 103
Scott, J. C., 478, 482
Scott, J. W., 256
Scott, M. L., 341
Scotti, T. M., 484
Scroggie, A. E., 441
Sealock, R. R., 341
Searle, L. M., 104
Sedan, J., 246
Sedenfciyan, A., 484
Seegers, W. H., 415, 441, 457
Seegmiller, J. E., 2, 360
Seeley, R. D., 58
Seevers, M. H., 457, 567, 573, 580
Segal, A., 126
Segal, G., 366
Segal, J., 254
Segaloff, A., 30, 90, 441
Segers, M., 390, 393, 395
Seguin, P., 510
Seibel, R. E., 453
Seidenari, R., 246
Seifert, J., 86
Seifter, J., 105
Seitz, C. F., 247
Selfridge, O., 395
Seligman, A. M., 92, 440, 512
Selkurt, E. E., 92, 406, 503
Selle, W. A., 110
Sellers, E. A., 86, 119
Selye, F., 453
Selye, H., 66, 69, 366, 451, 455
Selzer, A., 390
Semb, J., 341
Semenov, H., 241
Séquin, F., 124
Seraidarian, K., 314, 411
Service, D. M. G., *see* Graham-Service, D. M.
Setala, K., 533
Settlage, P., 271
Seymour, A. H., 530, 531
Seysenegg, A. v. T., *see* Tschermak-Seysenegg, A. v.
Shack, J., 335
Shadle, O. W., 435, 436
Shaffer, C. B., 86, 505
Shaffroth, M. D., 298, 302, 306
Shaflroff, B. G., 389
Shanes, A. M., 182, 307
Shank, R. E., 84, 85, 91
Shapiro, B., 509
Shapiro, K. L., 107
Sharafian, M. A., 478
Sharp, E. A., 94, 339
Sharpe G., 340
Sharpe, L. M., 121
Sharpey-Schafer, E. P., 400, 401, 402, 472
Sharples, W., 185
Sharpley, F., 256
Shaw, D., 219
Shaw, J. H., 67, 362
Shaw, W. A., 327
Shay, H., 83, 113, 128
Shea, P., 512
Sheard, C., 253, 444, 458
Shearer, E. M., 91
Shehata, O., 340
Sheldon, W. H., 87
Shemin, D., 89, 93, 335
Shen, S. C., 298, 315, 323
Sheppard, C. W., 120, 538
Sherber, D. A., 2, 32
Sherlock, S., 83, 84, 89, 91
Sherman, M., 124
Sherman, W. C., 115
Sherrod, T. R., 419, 575
Sherry, S., 63
Shettles, L. B., 24
Shideman, F. E., 577
Shimkin, M., 530
Shipley, R. A., 56, 90
Shipley, R. E., 405, 450
Shipton, H. W., 203, 208, 209, 216, 219
Shires, G. T., 469
Shive, W., 340
Shorb, M. S., 337
Shorr, E., 38, 71, 90, 92, 438, 449
Shoshkes, M., 126
Shpilberg, P. I., 222
Shukers, C. F., 336
Shute, E. V., 415
Shute, W. E., 415
Sibley, J. A., 247, 251
Sichel, F. J., 308
Siebenthal, B. J., 339
Siedel, W., 335
Siegel, P. S., 286, 287
Siegmund, O. H., 456, 470
Siemens, J. C., 222
Sievers, J. F., 561
Sigfried, D. A., 53
Signer, I. R., 552
Sillani, L. S., 479
Silva, J. A., 336
Silver, M. L., 214
Silver, S., 70
Simeone, F. A., 458, 570, 571
Simkin, B., 91, 405, 448, 471
Simkins, S., 57
Simmonet, H., 364, 365, 369, 373

Simmons, E. L., 531, 532, 533, 537
Simon, A., 572, 577, 579
Simon, A. P., *see* Perez Simon, A.
Simon, B., 222
Simonds, J. P., 510, 516
Simons, D. J., 222
Simonson, E., 249, 259, 308
Simpson, B. W., 56
Simpson, S. A., 3
Sims, E., 336
Sims, E. S., 336
Sinaiko, E., 389
Sinclair, D. C., 169, 217
Sinex, M., 478
Singer, E., 59
Singer, M., 312, 533
Singer, T. P., 528
Singh, I., 107, 298
Singh, S. I., 107
Sinubin, B., 405
Siplet, H., 83, 113, 128
Sjaardema, H., 221
Sjoerdsma, A., 419
Sjöstrand, T., 125, 144, 479
Skeggs, H. R., 508
Skipper, H. E., 341
Skoglund, C. R., 189, 190, 191
Skouby, A. P., 307
Skowron, W., 26
Slaughter, D., 253
Slein, M. W., 46
Slesinski, F. A., 85
Sloan, J. Q., 470
Sloan, L. L., 251, 253, 255, 256
Slocum, H. C., 447
Slome, D., 518
Small, L., 576
Smart, M., 327
Smelser, G. K., 37
Smirnova-Zamkova, A. I., 389
Smith, A., 92
Smith, A. E. W., *see* Wilder Smith, A. E.
Smith, A. U., 54
Smith, D. C., 69
Smith, E. C. B., *see* Bate-Smith, E. C.
Smith, E. E., 10
Smith, E. L., 12, 30, 337
Smith, F. W., 235
Smith, G. M., 247, 290
Smith, G. v. S., 27
Smith, H. W., 367, 453, 499, 501, 505, 506, 509
Smith, J. A., 63
Smith, J. R., 472
Smith, K. U., 274
Smith, M. H., 35
Smith, O. W., 27
Smith, P. E., 398
Smith, P. F., *see* Fremont-Smith, P.
Smith, P. K., 124
Smith, R. H. N., *see* Nimmo-Smith, R. H.
Smith, R. R., 575
Smith, S., 257
Smith, V. A., 360
Smith, W. H., 519
Smith, W. K., 162
Smithwick, R. H., 452
Smyth, J. B., 327
Snape, W. J., 94, 130
Snapp, F. E., 484
Snapper, I., 83
Snell, A. M., 83, 84
Snider, R. S., 16, 162, 164, 165, 530, 531, 535
Snow, S., 124
Snyder, C. H., 573
Snyder, F. F., 477, 484
Snyder, R. H., 537
Sobel, A. E., 124
Soberón, J., 409
Sobin, S., 451
Sobin, S. S., 451
Socoloff, E., 327
Sodi Pallares, D., 393, 409, 410
Sodi Pallares, E., 415, 416
Sokalchuk, A., 118, 470
Sola, A. E., 291
Sola, O. M., 327
Solandt, D. Y., 145, 256
Solans, A. H., 406
Sollman, T., 308
Sollner, K., 553
Solnitzky, O., 247
Soloman, K., 335
Solomon, E. I., 107
Solomon, H. G., 156
Solomon, R. L., 288
Soloway, E., 259
Sols, A., 121
Somkin, E., 475
Sommerville, I. F., 27
Somogyi, M., 62
Somolinos D'Ardois, G., 390
Sondermann, R., 246
Sonneborn, T. M., 3
Sonnemann, H., 202
Sonnenschein, R. R., 574
Sørensen, K. B., *see* Biering-Sørensen, K.
Soriano, V., 165
Sorsby, A., 245, 249
Soskin, S., 47, 420
Soslow, M. S., 390
Sosman, M. P., 400
Soukup, S. W., 38, 52
Soulairac, A., 50, 70, 104
Southworth, J. L., 444
Soviotti, G., 60
Spark, L. C., 315
Spear, F. G., 528
Specht, H., 470
Specter, M. E., 575
Speert, H., 38
Speirs, R., 364
Spencer, D. E., 251, 259
Spencer, J. N., 478
Spencer, W. P., 530
Sperry, R. W., 206 248, 274, 275, 276, 277
Spiegel, E. A., 162, 217
Spiegel-Adolf, M., 217
Spiegelman, S., 3
Spielman, M. A., 576
Spies, T. D., 337, 338, 339, 340
Spink, W. W., 346
Spinks, A., 124
Spinks, J. W., 536
Spitzler, R., 407
Spofford, W. R., 15
Sprague, R. G., 66
Spratt, N. T., Jr., 11
Springson, D. B., 186
Sproul, E. E., 89
Spühler, O., 410
Spurr, C. L., 376
Stacy, J. R., 574, 579
Stacy, R. W., 476, 484
Stadie, W. C., 47, 48
Stafford, R. A., 38
Stafford, R. O., 51
Stanbury, J. B., 119, 567, 569
Stanley, M. M., 59, 60, 61
Stansfield, H., 417
Stapleton, G. E., 529, 531
Stare, F. J., 83, 344
Starling, D., 341
Starr, I., 398
Stasney, J., 345
Stassi, M., 470
State, D., 127
Stavraky, C. W., 112

Stead, E. A., 397, 403, 423, 443, 444
Stead, E. A., Jr., 401, 402
Stearner, S. P., 532, 533
Stebbins, R. B., 362
Steele, C. W., 84
Steele, H. H., 83
Steggerda, F. R., 514
Steigmann, F., 111, 567
Stein, A., 257
Stein, G., 528
Stein, I. D., 443
Stein, J., 112
Steinbach, H. B., 298, 305, 323, 555, 557
Steinberg, A., 129
Steinberg, B., 86, 246
Steinberg, H., 110
Steinberg, M. E., 127
Steiner, A., 454
Steinkamp, R. C., 336
Steinman, J. F., 517
Steinwall, O., 216
Stellar, E., 288
Sten-Knudsen, O., 306, 324
Stenstam, T., 83
Stephenson, C., 217
Stephenson, H. U., Jr., 73
Stephenson, M. L., 72
Stern, C., 530
Stern, I. F., 127
Stern, K. G., 357
Sterner, J. H., 86
Stetten, D., Jr., 8, 62, 70
Stevens, C. D., 110
Stevens, H., 222
Stevens, M., 94
Stevens, S. S., 235, 241
Stevenson, J. A. F., 103
Stewart, A. M., 90
Stewart, D. R., 554
Stewart, H. C., 124
Stewart, H. L., 28
Stewart, L., 49
Stewart, P., 110
Stewart, R. D., 49
Stewart, W. C., 106
Stickney, J. C., 118, 120
Stiles, W. S., 253, 258
Stilson, C., 53
Stimmel, B. F., 31
Stocker, F. W., 247
Stockholm, M., 509
Stoerk, H. C., 66, 361, 362, 374, 375, 377
Stokes, J., Jr., 377, 379
Stokes, J. F., 84
Stokstad, E. L. R., 338, 339, 340, 341
Stoll, R., 6
Stone, C. P., 279, 280, 281, 282, 283
Stone, D., 304, 364, 370
Stone, F., 103
Stone, R. E., 337, 339, 340
Stone, R. S., 529
Stool, R., 14
Stotler, W. A., 141
Stout, A. P., 140
Strait, L. A., 298, 302, 306
Strajman, E., 477
Strangeways, D. H., 477
Straub, J., 547, 549, 552
Straus, O. H., 574, 575, 576, 577, 579
Straus, W. L., 15
Strauss, H., 217
Street, S. F., 304, 305
Streicher, D., 92
Strell, M., 335
Strohl, A., 178
Ström, G., 110
Strong, L. C., 4, 5
Stroud, M. W., 410, 416
Strumza, M. V., 478, 479, 480, 483
Stubbs, A. L., 31, 250
Stubbs, J., 480
Stuckey, H. L., 286
Studnitz, G. v., 252
Stuhl, L., 218
Sturgeon, M., 106
Sturgis, C. C., 338
Sturm, E., 368, 376
Sturm, H., 476
Stutz, V., 359
Stutzman, J. W., 152, 153
Suarez, J. R. E., 401
Suárez, R. M., 338
Suárez, R. M., Jr., 338
Subbarow, Y., 341, 448
Suckle, H. M., 214, 572
Suffern, W. S., 85
Suffolk, S. F., 147
Sugar, O., 163, 164, 207, 208
Sulkin, N. M., 140
Sullivan, W. E., 327
Sullivan, W. H., 527
Sullman, H., 246
Sulman, F., 26, 34, 35
Sulzbach, W. M., 391
Sulzer, R., 410
Sundberg, R. D., 346
Sunderland, S., 140
Suner, A. P., *see* Pi Suner, A.
Surtshin, A., 69, 393, 458, 473, 570
Suskind, M., 474
Suskind, M. I., 327
Sussman, A. H., 475
Suter, G. M., 532
Sutherland, E. W., 48
Sutherland, V., 572, 577, 579
Sutler, M. R., 567
Suttel, R., 219
Svarvos, P., 312
Svensson, H., 550, 553
Sverdlov, Z. M., 254
Svirbely, J. L., 85
Swan, R. C., 509
Swank, R. L., 484
Swann, H. G., 459
Swanson, A. L., 341
Swanson, C. P., 529
Swanson, M. A., 123
Sweeney, J. S., 83
Swendseid, M. E., 340,341
Swenson, P. C., 107
Swenson, R. E., 53
Swift, M. N., 367, 529, 531, 535, 536
Swinyard, E. A., 212, 214
Swyer, G. I. M., 2, 31, 32
Sydenstricker, V. P., 245
Sykes, E. M., Jr., 441
Sylvester, M., 66
Sysa, J., 484
Szego, C. M., 30, 90, 361, 366, 375
Szekeres, G., 259
Szent-György, A., 311, 313, 315, 316, 317, 320, 323, 324, 325, 326, 412
Szepsenwol, J., 308, 391, 409

T

Tagnon, H. J., 83, 512
Tainter, M. L., 147, 572
Talbert, G. B., 38
Talbot, D., 327
Talbot, N. B., 68
Talbot, S. A., 247
Talbot, T. R., 470, 475
Talenti, C., 470
Talesnik, J., 56, 150, 416
Talmage, R. V. N., 28
Talso, P. J., 453
Talso, P. L., 497
Tamalet, J., 218
Tansley, K., 251

Taquini, A. C., 401
Tarr, R. R., 374
Tatting, B., 340
Taurog, A., 53, 54, 55
Taussig, H., 389
Taussky, H. H., 494
Tavares Bastos, A., 199
Tavel, F. von, 484
Tavel, P. von, 552
Taylor, A., 8
Taylor, A. N., 458
Taylor, B., 528
Taylor, C. B., 477, 484
Taylor, D. B., 566
Taylor, F. H. L., 84, 512
Taylor, H. C., Jr., 92, 442
Taylor, H. L., 106, 447
Taylor, K. W., 11
Taylor, R. D., 452, 453, 458, 566, 567, 568
Taylor, R. M., 222
Taylor, W. O. G., 245
Teagley, J. D., 128
Tejerina-Fotheringham, W., 117
Tejning, S., 62
Templeton, F. E., 106
Ten Cate, J., 191
Tendle, M. J., 514
ten Doesschate, G., 257
ten Doesschate, J., 254
Tenney, M., 495
Teorell, T., 109, 297, 547, 549, 551, 552, 553, 555, 558, 559, 561
Tepperman, H. M., 34
Tepperman, J., 34
Teresi, J. D., 527, 537
Terner, C., 108, 109
Terroux, K. G., 391
Terry, P., 29
Tetelbaum, A. G., 478
Teuber, H. L., 255, 260
Teuber, L., 260
Thannhauser, S. J., 9
Theobald, G. W., 125
Theobald, J., 203
Thérien, M., 103
Therman, P. O., 189, 190, 191
Thienes, C. H., 416
Thiersch, J. B., 360
Thiesen, J. W., 202
Thomas, C. B., 477
Thomas, G., 494
Thomas, I. A., 368
Thomas, J. E., 116, 117, 130
Thomas, R. W., 458
Thomasen, E., 324
Thompson, F. L., 83
Thompson, L. C., 258
Thompson, M. D., 123
Thompson, P. K., 60
Thompson, S. A., 437
Thompson, S. Y., 29
Thompson, W. O., 60
Thompson, W. W., 327
Thomsen, P., 327
Thomson, A., 12, 30
Thomson, J. D., 59, 327, 359
Thomson, L. C., 248
Thorell, B., 346, 359, 360, 378
Thorn, G. W., 68, 91, 370, 374
Thorne, S. O., Jr., 327
Thorp, R. H., 574, 575, 576
Thorp, W. T. S., 33
Thorpe, W. H., 484
Threefoot, S., 401
Tidwell, H. C., 85
Tieche, H. L., 567
Tiffany, B. D., 576
Tilden, J. H., 450
Timm, C., 482
Tinsley, M., 495
Tipton, I. H., 52
Tipton, S. R., 52
Tissières, A., 52, 359
Titeca, J., 186
Tobias, C. A., 529
Tobias, J. M., 176, 308
Tobias, M., 184
Toca, R. L., 337, 339
Toczyski, T., 484
Todd, A., 152
Todd, J., 327
Todd, R. L., 448
Todd, W. R., 64
Tolman, L., 341
Tolpin, M., 459
Toman, J. E. P., 184, 185, 212, 214
Tomarelli, R. M., 86
Tompkins, P. C., 527
Tønnesen, M., 31
Torbet, N., 340
Torda, C., 304, 315, 327, 418
Torok, M. G., *see* Gajdos-Torok, M.
Torpin, R., 27
Torrance, R. W., 481
Torre, J. M., 409
Toselli, C., 248
Totter, J. R., 336
Tousey, R., 248, 249
Tove, S. B., 344
Tovee, E. B., 129
Townsend, S. E., 394
Traut, E. F., 346
Traut, H. F., 38
Trautman, W. J., 416
Trautman, W. J., Jr., 449
Travis, R. C., 327
Treadwell, C. R., 85
Treleaven, C. L., 248
Trent, S. E., 260
Tripi, H., 60
Tripp, E., 442, 449
Trocme, C., 410
Troell, L., 119
Trowbridge, C., 304
Troxil, E. B., 574, 576, 579, 580
Trucco, E., 57
Trucco, R. E., 47
Trueta, J., 451, 496
Truex, R. C., 388
Tschermak-Seysenegg, A. v., 248
Tschumi, H., 511
Tsuker, M., 143
Tuba, J., 50
Tucker, A. L., 116
Tulin, M., 113, 555, 556, 557
Tullar, B. F., 147, 572
Tullis, J. L., 554
Tumarkin, A., 233
Tunturi, A. R., 237, 239
Turkel, M., 305
Turman, W. G., 388, 408
Turner, O. A., 216
Turner, R. S., 183
Turpin, R., 327
Tuttle, W. W., 444
Tweed, P., 406
Tweedy, W. R., 72
Tyler, D. B., 215, 216, 291
Tyree, E. B., 367, 529, 535, 536

U

Ubatuba, F., 344
Uchiyama, J. K., 577
Ucko, H., 55
Ukeyama, K., 85
Ullyot, G. E., 576
Underwood, L. C., 567
Ungar, G., 360
Ungerleider, H. E., 390

Ungewitter, L., 499
Unna, K. R., 106
Ussing, H. H., 555, 557
Utterback, R. A., 142
Uvnäs, B., 110, 113, 114, 154
Uxova-Khynova, A., 253
Uyldert, I. E., 35

V

Vacca, C., 475, 478, 484
Vail, D., 247
Vail, V. N., 50
Valdecasas, F. G., 57
Valdés, R., 122
Valencia, F., 408
Valentine, E. H., 348
Valentine, W. N., 370, 371, 373, 533, 534
Valk, W. W., 567
Valkó, E. I., 553
Valle, J. E. do, *see* do Valle, J. E.
Valle, J. R., 35
Vallon, S. B., *see* Braun-Vallon, S.
Van Campenhout, E., 15, 16, 139
Van Cleave, C. D., 15
Vandam, L. D., 398, 400, 448, 471
Vandenberg, H. J., Jr., 128, 130
van den Brock, W. A., 121
Vandenbroeck, J., 62
van der Horst, L., 199
VanderLaan, W. P., 55
Van der Velden, H. A., 254, 255
Vander Werff, H., 340
van der Werff, J. T., 528
Van Dooren, F., 395
van Eijk, M., 547, 549, 552
Van Harreveld, A., 194, 212, 327, 569
Van Heerswynghels, J., 395
Van Liere, E. J., 107, 118, 120
Van Middlesworth, L., 447
Van Milaan, J. B., 410
Van Slyke, D. D., 439, 440, 496, 500, 501, 508, 512, 515, 516, 518, 519
Van Straaten, J. J., 247
Van Wagenen, G., 26
van Wagtendonk, W. J., 3
Van Waters, R. O., 272
van Weel, P. B., 10
Vanzant, R. F., 129
Vanzetti, G., 246
Vara, P., 410
Varga, L., 318, 319, 320
Vars, H. M., 89
Vartiainen, I., 104
Vass, C. C. N., 125, 144
Vaughan, J., 345
Vaughan, S. L., 346
Vavilov, S. I., 254
Veen, H., 469
Véghelyi, P., 107, 116
Veldman, H., 121
Velez Orozco, F., 416
Venning, E. H., 68
Verbeke, R., 484
Verdeaux, G., 199, 217, 219
Verdeaux, J., 199, 217
Verne, J., 49
Verney, E. B., 152
Verney, E. L., 103
Verspyck, H., 218
Verzár, F., 359, 478, 479
Vescia, A., 477
Vezian, B. L., 459
Vial, J., 153, 482, 483
Viale, S. M., 217
Viergiver, E., 32
Vigneaud, V. du, *see* du Vigneaud, V.
Ville, C. A., 4
Vilter, C. F., 338
Vilter, R. W., 338
Vilter, V., 247
Vinokurov, V. A., 483
Viollier, G., 246
Visscher, F. E., 114
Visscher, M. B., 108, 308, 448, 471, 475
Viteles, M. S., 260
Vivino, A. E., 569
Vivone, F. R., 57
Vleeschhouwer, G. R. de, *see* de Vleeschhouwer, G. R.
Voegtli, W., 478
Vogel, H., 472
Vogel, P. J., 252
Vogelsang, A. B., 415
Vogelsang, T. M., 12
Vogt, M., 67, 150
Vogt, O., 359
Volk, D., 258
Volovartz, K., 89
Volwiler, W., 91
von Békésy, G., 231, 232, 240, 241
von Bonin, G., 162, 163
Von Bonsdorff, B., 339
Vonderahe, A. R., 164
Vonder Heide, E. C., 339
von Dobeneck, H., *see* Dobeneck, H. v.
von Euler, C., *see* Euler, C. v.
von Euler, H., *see* Euler, H. v.
von Euler, U. S., *see* Euler U. S. v.
von Falkenhausen, 84
von Gierke, H., *see* Gierke, H. von
Vonotzky, J., 103
von Studnitz, G., *see* Studnitz, G. v.
Von Sullman, H., 245
von Tavel, F., *see* Tavel, F. von
von Tavel, P., *see* Tavel, P. von
Vosburgh, G. J., 27, 28
Vuylsteke, C. A., 63

W

Wachstein, M., 89
Waddell, M., 203
Waddell, W. E., 574, 575, 576, 577, 579
Waddington, C. H., 15
Wade, L., 85
Wade, M., 271
Wade, N. J., 35
Wagenaar, J. W., 259
Wagley, P. F., 338
Wagman, I. H., 248
Wagner, R., 360
Wagtendonk, W. J. van, *see* van Wagtendonk, W. J.
Wahi, P. N., 86
Wajda, H. S., 327
Wakerlin, G. E., 566, 570
Wakim, K. G., 327, 442
Walcott, W. W., 437, 440
Wald, G., 249, 250, 253, 255
Waldenström, J., 339, 341
Waldman, M. S., 412, 416
Waldo, C. M., 12, 37
Waldron, J. M., 124
Walker, A. E., 214, 217, 218, 221
Walker, B. S., 344

Walker, C. F., 215, 219, 222
Walker, D. M., 29
Walker, E., 477
Walker, H. A., 457, 573
Walker, P., 396, 477
Walker, S. M., 195, 298, 301, 302, 303, 308
Walking, A. A., 89
Wall, A. G., 415
Wallach, H., 253
Waller, C. W., 341
Walls, E. W., 387, 391
Walsh, E. G., 152, 252, 481
Walsh, F. B., 73
Walsh, R., 248
Walshe, F. M. R., 164
Walshe, V., 84, 89, 91
Walter, V. J., 199, 208, 209, 210, 211, 215, 219, 220, 222
Walter, W. G., 191
Walter, W. Grey, 199, 200 201, 202, 203, 204, 205, 208, 209, 210, 211, 215, 216, 218, 219, 220, 222, 223
Walters, G. R., 495
Walters, J. H., 115
Waltner, J. G., 235
Walton, E., 574, 575, 576
Walton, R. P., 421
Waltzer, F., 440
Walzl, E. M., 237, 240
Wandruff, B., 341
Wang, C. C., 116
Wang, H., 23
Wang, J.-C., 246, 559
Wang, S. C., 144, 145, 437, 479, 482
Wangensteen, O. H., 91, 127
Ward, A. A., 207, 271
Ward, A. A., Jr., 155, 162, 163, 167, 168, 208, 211, 214
Ward, J. W., 217, 448
Ward, S. M., 84
Warden, H. F., 338
Ware, A. G., 441, 457
Ware, P. A., 578
Waridel, A., 327
Warkany, J., 5
Warner, L., 91, 459
Warren, J. V., 397, 398, 400, 401, 402
Warren, S., 86, 532
Warren, S. L., 532
Warrens, A. E., 579
Warwick, E. J., 23
Wasserman, A., 323
Wasserman, L. R., 529
Wastl, H., 452
Waterlow, J. C., 84
Watkins, A. L., 327
Watkins, C. H., 338, 341
Watkins, W. M., 389
Watkinson, J. M., 368
Watson, C. J., 92, 93, 335, 336, 533
Watson, C. W., 215, 222
Watson, D. W., 358
Watson, E. M., 53
Watson, G. M., 346
Watts, J. W., 162, 272
Weatherall, J., 473
Webb, E. A., 440, 458
Webb, J. L., 416
Webb, J. P., 212
Webster, M. R., 118
Webster, T. A., 88
Wechtel, C., 84
Wedd, A. M., 421
Weddell, G., 169, 217, 327
Weekers, R., 255
Weel, P. B., van, *see* van Weel, P. B.
Wégria, R., 407, 458
Weiden, S., 453
Weidmann, W., 249
Weil, A. A., 201, 222
Weil, R., 70
Weinberg, S. J., 410
Weiner, D., 445
Weiner, H. M., 472
Weinstein, H. R., 63
Weinstein, M., 389
Weintraub, H. J., 407
Weir, D. R., 368
Weir, J. F., 83, 338
Weisberger, A. S., 338
Weiss, H. A., 85
Weiss, J., 528
Weiss, M., 309
Weiss, P., 13, 327
Weissman, N., 358
Welander, A. D., 530, 531
Welch, A. D., 338, 339, 340
Wells, J. A., 571
Wells, L., 154
Wells, L. J., 33
Werff, H. V., *see* Vander Werff, H.
Werff, J. T., van der, *see* van der Werff, J. T.
Werko, L., 401, 472, 474
Wersäll, R., 559
Wertheimer, E., 65
Wescoe, W. C., 84, 341
Wesson, L. G., 509
West, E. S., 495
West, G. B., 146, 572
West, J. R., 499, 505, 509
West, R., 51, 93, 337
West, W. J., 444
Weston, R. E., 370, 476, 478
Westphal, U., 479
Wever, E. G., 235, 236, 237
Wexler, J., 396
Weymouth, F. W., 249, 257
Weymouth, P. P., 529
Wheatley, M. D., 163
Whedon, G. D., 71
Wheeler, C. E., 68
Wheeler, E. O., 445, 448
Wheeler, J. E., 85
Wheeler, N. C., 397
Whewell, C. S., 323
Whidborne, J., 93
Whipple, A. O., 91
Whipple, G. H., 121
White, A., 58, 66, 357, 358, 359, 360, 361, 363, 364, 365, 366, 368, 369, 370, 371, 373, 374, 375, 376, 377, 379
White, B. H., 119
White, F. R., 362
White, H. L., 70, 397, 399, 497, 504
White, J., 362
White, J. C., 142
White, P., 50
White, P. D., 390
White, W. C., 119
White, W. F., 420, 421
Whiteacre, W. M., 219
Whitehair, C. K., 344
Whitehead, B. W., 509
Whitehead, R. W., 478
Whitehorn, W. V., 469
Whitelaw, M. J., 61
Whiteleather, J. E., 473
Whitfield, I. C., 435
Whitrock, R. M., 119, 567
Whittaker, N., 339
Whittenberger, J. S., 396
Whitteridge, D., 153, 199, 202, 204, 213, 214, 216, 443, 474, 480, 481
Whittier, J. R., 167
Whitty, C. W. N., 222

Whorton, C. M., 573
Wick, A. N., 114, 128
Wicklund, E., 1
Wiebelhaus, V. D., 59
Wiener, N., 205, 278, 395
Wiercinski, F. J., 305, 318, 319
Wierama, C. A. G., 194, 327, 569
Wierzuchowski, M., 484
Wiese, C., 57
Wiesinger, K., 478, 484
Wiggers, C. J., 92, 143, 399, 470, 482
Wiggins, M. L., 154
Wijga, P. W. O., 553
Wikler, A., 221, 574, 575, 576, 577, 578, 580
Wilber, D. T., 304
Wilbrandt, W., 297, 555, 557
Wilburne, M., 396, 441, 458, 570
Wilde, J. H., 547, 549, 552
Wilde, N. J., 143
Wilde, W. S., 28, 246, 555, 560
Wilder, J., 64
Wilder Smith, A. E., 31
Wilhelmi, A. E., 71, 92, 366, 439
Wilkins, R. W., 442, 443, 573
Wilkinson, J. F., 338, 339
Williams, A. H., 496
Williams, D., 218, 223
Williams, E. M. V., 508
Williams, H. H., 8
Williams, P. C., 2, 33
Williams, P. E., 86
Williams, R. H., 90
Williams, R. T., 31
Williams, T. L., 83
Williams, W. L., 86, 390
Williamson, M. B., 57
Williamson, M. D., 5
Williamson, R. C., 499
Willner, M. D., 156, 218
Wills, J. H., 457
Wills, L., 339
Wilson, A., 327
Wilson, C., 84
Wilson, C. W., 528
Wilson, F. N., 410
Wilson, H. A., 529
Wilson, J. L., 580
Wilson, J. W., 88
Wilson, M., 59
Wilson, R. H., 458
Wilson, W. H., 481
Wilson, W. L., 327
Winans, H. M., 410
Winbury, M., 417
Winder, C. V., 458
Windle, W. F., 291
Winkler, A. W., 59, 60, 400, 506, 508, 510
Winnick, T., 72
Winsor, T., 396, 441
Winter, C. A., 128
Winterstein, H., 482, 484
Wintrobe, M. M., 335, 336, 337, 340, 345
Winzler, R. J., 57
Wirth, J. E., 527, 535
Wirts, C. W., 94
Wirz, E., 477, 484
Wise, C., 398
Wise, C. S., 445
Wise, G. H., 13
Wise, W., 415
Wiseman, B. K., 538
Wiskovský, B., 250
Wislocki, G. B., 12, 37, 312, 360, 361
Wissler, R. W., 374, 377
With, T. K., 92, 93, 94
Witham, A. C., 397
Witherup, S., 494
Witkin, E. M., 530
Witschi, E., 14
Witts, L. J., 87, 90
Wixom, R., 68
Wolcott, W. W., 402
Wolf, A. V., 508
Wolf, S., 112, 113, 481
Wolferth, C. C., 410
Wolff, E., 248
Wolff, E(milienne), 14
Wo!ff, E(tienne), 7, 14
Wolff, H. G., 112, 113, 168 304, 315, 327, 418
Wolff, J., 55
Wolfson, W. Q., 495
Wolkowitz, W., 536
Wollack, A. C., 476
Wollaeger, E. E., 117, 126
Wollenberger, A., 411, 414, 419, 420
Wollin, D. G., 400
Wolvekamp, H. P., 478
Wong, C. C., 510
Wood, E. H., 477, 484, 566
Woodbury, J. W., 184, 185
Woodbury, L. A., 68, 184 185
Woodhall, B., 217, 218
Woodruff, C. W., 341
Woods, H. J., 322, 323
Woodward, A. A., 327
Woodward, A. A., Jr., 305, 318
Woodward, E. R., 129
Wooley, J. G., 344
Woolf, J. I., 218
Woolley, D. W., 341
Woolsey, C. N., 161, 164, 199, 237, 240
Wootton, I. D. P., 477
Worth, H. M., 484
Worth, W., 345
Wortis, S. B., 566
Wright, C. S., 348, 538
Wright, H. E., 511
Wright, L. D., 508
Wright, M., 418
Wright, R. R., 388
Wright, W. D., 250, 252, 255, 258, 259
Wu, H. C., 448
Wulff, V. J., 251
Wycis, H. T., 162, 217
Wyman, J., 307
Wyss, F., 471, 494
Wyss, O. A. M., 481, 482
Wyssling, A. F., *see* Frey-Wyssling, A.

Y

Yamshon, L. J., 327
Yanz, N., 419, 420
Yeager, L. B., 510
Yeagley, J. D., 567
Yeates, N. T. M., 36
Yee, H., 59
Yeshoda, K. M., 344
Yntema, C. L., 15, 16, 140
Yoffey, J. M., 363, 370
Yonkman, F. F., 105, 571
Youmans, W. B., 144, 147, 148, 151, 458, 571
Young, F. G., 65
Young, L. E., 83
Young, N. F., 66
Young, P. T., 289
Yuen, D. W., 497
Yuile, C. L., 517
Yuska, H., 511

Z

Zable, M., 271
Zajaczek, S., 26
Zak, F. G., 89

Zamecnik, P. C., 72
Zamfiresco, M., 92
Zamkova, A. I. S., *see* Smirnova-Zamkova, A. I.
Zapp, J. A., Jr., 47
Zawadski, B., 310
Zbinden, F., 451
Zeit, W., 143
Zevin, S. S., 214
Ziegenhagen, A. J., 413
Ziering, A., 575
Zierler, K. L., 66
Zilversmit, D. B., 123
Zimmerman, F. T., 217
Zinberg, S., 475
Zipkin, I., 105
Zirkle, R. E., 529, 531
Ziskind, E., 221
Zondek, B., 26, 27, 34, 35, 90
Zotterman, Y., 143, 144
Zubin, J., 283
Zucker, T. F., 361
Zuckerman, S., 25
Zuelzer, W. W., 339, 346
Zweifach, B. W., 92, 438, 449, 560
Zweig, M., 111, 567
Zwemer, R. L., 67
Zwilling, E., 6
Zygmuntowicz, A., 68

SUBJECT INDEX

A

Acetyl-β-methylcholine
  arterial pressure and, 156
Acetylcholine
  brain electrical activity and, 207–8, 213–14
  calcium and, 456
  cardiac stimulation by, 417–18
  cardiac vagal impulses and, 417
  circulation time and, 441
  endometrium, estrogens and, 26
  fibrillation and, 393
  gastric mucosa and, 112–13
  heart muscle and, 392–93
  intestinal muscle stimulation and, 150
  intestinal synthesis of, 119
  lymphopenia and, 372
  muscle conduction and, 309
  nerve conduction and, 184–85
  neuromuscular junction and, 195
  synaptic transmission mediation and, 194
  temperature and, 459
  tetraethylammonium and, 565
  thyroid and, 56
Acids
  excretion of, 507
  fatty
    oxidation of, heart muscle and, 412
    synthesis of, 126
  see also particular acid
Actin
  in muscle, 313
Activity, muscular, *see* Muscular exercise
Actomyosin
  adenosinetriphosphatase and, 315–16
  complex, 313
  contraction of, 316–26
    adenosinetriphosphatase and, 316–18
    endothermic reaction and, 320
    temperature and, 318
Adenosinetriphosphatase
  activity coupling role of, 323–25
  actomyosin solutions and, 315–16
  functions of, 323–24
  muscle contractile energy and, 314
  properties of, 314
Adenosinetriphosphate
  heart and, 411–12
  insulin and, 48
Adrenal cortex, 64–69, 455
  cortical hormone synthesis and, 66–67
  extract of
    anamnestic response and, 375–76
Adrenal cortex (*cont.*)
  extract of (*cont.*)
    blood globulin and, 373–75
    blood lymphocytes and, 369–73
    carbohydrate utilization and, 65
    glucose and, 64
    lymphoid tissue and, 363–65
    splenic lymphocytes and, 371
  fat metabolism and, 65
  lipids of, 67
  pituitary control of, 68–69
  protein metabolism and, 65–66
  radiation and, 366–67
  secretion of, 67
  steroids of
    nucleic acids and, 359–60
  see also Corticosterone, Desoxycorticosterone, etc.
Adrenal glands
  Addison's disease, 66
  adrenalectomy
    lymphoid tissue and, 361
    serum proteins and, 375
  lymphoid tissue involution and, 362
  radiation and, 535–36
Adrenal medulla, 69–70, 455–56
  secretion by, 70
Adrenaline, *see* Epinephrine
Adrenochrome
  epinephrine activity and, 69
Adrenocorticotropin
  see Pituitary, anterior, adrenotrophic hormone
Adrenolytic agents, *see* Dibenamine, Dihydroergocornine, etc.
Aerosols
  lung penetration by, 470
Age
  brain electrical activity and, 216
  carbon monoxide desaturation and, 477
  lymphoid tissue and, 362–63
  spleen and, 362
Albumin, serum
  renal function and, 502
Alcohol
  fatty livers and, 85–86
  nerve conduction and, 182
Allantoin
  glomerular filtration and, 505
Alloxan
  phosphatase and, 50
Allyl formate
  liver injury and, 86
Amino acids
  cornea and, 245

Amino acids (*cont.*)
hormones and, 71
insulin and, 63–64
intestinal motility and, 118
thyroid gland and, 58
Aminohippurate
renal blood flow and, 500–1
renal tubular function and, 509
Aminopyrine
absorption of, 124
Ammonia
renal excretion of, 508
Amphetamine
appetite and, 103–4
behavior and, 215, 291
electrical activity and, 215
Amyl nitrite
heart and, 396
Amytal
behavior and, 291–92
Analgesics
activity of, 573–78
synthetic, 573–80
see also specific substances
Androgens
androgenic control, 37
antler growth and, 37
chick embryo brain and, 6
chromosomes and, 366
embryonic sex differentiation and, 14
estrogen implants and, 25
feminizing effects of, 14
phosphatase activity and, 50
reviews on, 38
sebaceous glands and, 37
thymus and, 366
turgescence and, 25
Anemia
casein and, 344
cobalt and, 345
erythrocyte protoporphyrin and, 337
macrocytic
pteroylglutamic acid and, 340
pernicious
pigment and, 337–38
pteroylglutamic acid and, 338
vitamin B_{12} and, 337
reticulocytosis and, 343
steatorrhea and, 123
yttrium and, 537
Anesthetics
nerve excitation and, 181–82
Angiotonin
hypertension and, 449
properties of, 455
Anoxia, *see* Oxygen deficiency
Antacids
gastric secretions and, 111
Anterior hypophysis, *see* Pituitary
Antibodies
absorption of, 124
adrenal cortical extract and, 376
anamnestic response, 375–76
formation of
lymphocytes and, 376–78
macrophages and, 378
plasma cells and, 378
pyridoxine and, 377–78
site of, 378–80
thymus and, 377
vitamin deficiency and, 378
irradiation and, 534
Antigens
anamnestic response and, 379–80
in embryonic blood, 12–13
in embryonic developmental stages, 13
lymphocytes and, 377
lymphopenia and, 372
ulceration and, 127
Antigonadotrophins, 35
Anuria
kidney damage and, 515
Aorta
capacity of, 459
Apyrase activity
in embryonic development, 9
Arginase, 49–52
adrenalectomy and, 50
estrogens and, 50
of mammary gland, 51
in red cells, 51–52
Arginine
heart and, 417
Argon
penetration of, 477
Arterial pressure
acetyl-β-methylcholine and, 156
basal metabolic rate and, 453
cardiac output and, 402
dihydroergotamine and, 572
frontal lobe stimulation and, 156
hypertension and, 451, 453
measurement of, 448
medulla oblongata and, 153
methadon and, 577
posture and, 449
pulmonary, 471–72
renal blood flow and, 503
spinal nerve stimulation and, 142
systolic, 459
tetraethylammonium and, 566
values of, 448–49
see also Vasomotor phenomena
Arteries
flow in, 458
Ascites
hepatic lymph and, 91
plasma protein and, 91

Ascorbic acid
of adrenal cortex, 67
of corpora lutea, 67
excretion of, 509
of leukocytes, 360
in the placenta, 8
Aspirin
absorption of, 124–25
Atherosclerosis
blood colloidal particles and, 454
etiology of, 454
hypercholesteremia and, 454
lipophage cells in, 454
Atropine
gastric secretion and, 111
pancreas and, 116
Autonomic nervous system, 139–60
drugs and, 456–58, 567–73

B

Bacitracin
glomerular filtration and, 505
Bacteria
lymphocytes and, 368
Barium
cardiac activity and, 412
intestinal muscle and, 150–51
nerve rhythmic activity and, 180
radioactive, 537
vagal stimulation and, 150
Basophilia
in lymphocyte cytoplasm, 359–60
Benzene
liver damage and, 85
Bicarbonate
gastric secretion and, 111–12
Bile
composition of
salts and, 94
fat absorption and, 123
pancreatic necrosis and, 117
Bile acids
biliary excretion of, 94
Biliary fistula
external, 94
Bilirubin
blood globulins and, 93
direct and indirect, 93
in fistula bile, 94
liver injury and, 356
production and elimination of, 92
renal threshold for, 92
Biotin
in egg
sucrose and, 5–6
Bladder, urinary
distention of
spinal cord lesions and, 153
hypothalamic stimulation and, 154
Bladder, urinary (*cont.*)
tetraethylammonium and, 567
Blood
arterial
oxygen and, 477
clotting of, 441
heparin and, 445
intravascular, 445
spleen and, 360
see also Heparin and Platelets, blood
cutaneous
venules and, 443
embryonic
constituents of, 12–13
flow
anesthesia and, 444
arterial occlusion and, 444
cold and, 445
denervation and, 444
dihydroergotamine and, 572
epinephrine and, 443
in fingers, 443
intravenous infusions and, 446
in legs, 442–43
measurement of, 442
pulmonary, 460
gas analysis of, 484
hematopoiesis, 335–54
oxygen capacity determination of, 477
oxygen tension of, 478
platelets, *see* Platelets, blood
pressure, *see* Arterial pressure
pressure breathing and, 473
respiratory gas exchange and, 478
saline absorption and, 120
sludged, 459
substances in, *see* specific substances
volume
in children, 436–37
distribution of, 437
estimation of, 435–36
see also Circulation, Hemoglobin, etc.
Bone
parathyroids and, 73
plutonium and, 537
radium and, 537
structure of
growth rates and, 16
thyroid and, 56
Bone marrow, 345–48
cells of, 346
cellular proteins of
ribose polynucleotide and, 347
estrogens and, 343–44
metabolism of, 346
myelograms, 346
oxygen tension and, 346
radiation and, 532–33
spleen and, 348

Brain
brain stem
epileptic seizure and, 166
petit mal seizure and, 166
spasticity and, 167–68
tremor and, 167
corpus callosum section
reaction time and, 275
electrical activity of, 199–230
acetylcholine and, 213–14
age, maturation and, 216
alcoholic intoxication and, 212
analysis of records of, 201–3
anoxia and, 212–13
asphyxia and, 212–13
cellular hydration and, 212
corticobasal connection and, 211
drugs and, 214–15
emotion and, 216–17
epilepsy and, 218–22
genetics and, 215–16
hypnosis and, 206–7
hypoglycemia and, 212–13
learning and, 273–74
lesions and, 217–18
mental disorders and, 222
pentothal and, 213
recorders of, 200–1
reviews on, 199, 222
sleep, fatigue and, 216
spontaneous activity and, 203–6
stimulation and, 208–10
subcortical activity and, 208
suppression of, 206–8
thalamus stimulation and, 211
trauma and, 217
glucose uptake by, 554
glycolysis of, 46
hexokinase activity of, 46
injury of
intelligence and, 273
methadon and, 579
neocortex removal, 274
olfactory regions of, 162–63
pain and, 217
porencephaly, 217
prefrontal lobectomy
learning loss and, 271
prefrontal lobotomy
schizophrenia and, 272
radiation and, 536
sympathomimetic amine in, 147
temperature and, 459
see also Cerebellum, Cerebral cortex, Medulla oblongata, etc.
Bromosulfalein
hepatic blood flow measurement and, 92
Bromsulphonphthalein
hepatic blood flow and, 442
Burn shock, 439

C

Caffeine
cellular metabolism and, 2
gastric secretion and, 115
Calcium
absorption of, 120
acetylcholine stimulation and, 456
gastric secretion and, 111–12
metabolism of, 73
muscle contraction and, 318
nerve membrane potential and, 180
thyroid and, 56
Cancer, *see* Tumors
Capillaries
diffusion in, 551
permeability of, 356, 560
Caprylate
heart and, 412
Carbinols
analgesic activity of, 575
Carbogen
resuscitation and, 478
Carbohydrates
appetite and, 104
in fetal blood, 13
gastric emptying time and, 107
in heart muscle, 414
metabolism of
adrenal cortex and, 64–65
endocrines and, reviews on, 64
hypothalamic-pituitary paths and, 70–71
insulin and, 45–49
pancreas and, 61–64
radiation and, 536
thymus and, 359
see also specific substances
Carbon dioxide
alveolar, 475–76
in blood, 478
cornea and, 245
electrocardiography and, 410
elimination of
bicarbonates and, 478
fetal respiration and, 479
gravity and, 447
hypertension and, 453
intestinal motility and, 118–19
lung volume and, 479
nerve membrane potential fraction and, 177
pulmonary capillary blood flow and, 471
pulmonary ventilation and, 479
vasoconstrictor center and, 154
Carbon monoxide
desaturation, age and, 477
Carbon tetrachloride
hepatic damage and, 86
Carcinoma, *see* Tumors

Cardiac output, 395–405
breathing and, 401
coronary flow and, 406–7
exercise and, 398
heart failure and, 401
hemorrhage and, 402
histamine and, 399
hypophysectomy and, 399
measurement of, 397
pressure breathing and, 474
tamponade and, 401
venous pressure and, 398–99, 403–5
ventricular dynamics and, 402
Carotene
absorption of, 124
Carotenoids, *see* Vitamin A
Carotid sinus
nerve of
stimulation of, 151
reflexes of, 144–45
Casein
anemia and, 344
Catalase
pernicious anemia and, 341
Cells
electrical potential in, 549
permeability of, 553–61
water transfer and, 555–56
Cerebellum, 164–66
cerebrocerebellar interrelations, 165
facilitation and, 165
lesions of, 166
suppressor areas of, 164–65
tremor and, 167
Cerebral cortex, 161–64
auditory
ablation of
response discrimination and, 240
sound conditioning and, 238–39
effector areas of
archicortex, 162–63
functions of, 161
occipital, 164
somatic, primary and secondary, 163–64
temporal, 164
frontal lobectomy and, 156
hypothalamic nuclei and, 155
intrinsic activity in
thalamus and, 161
prefrontal cortex, 162
prefrontal lobotomy, 156
pupillary dilatation and, 155–56
thalamus and, 278
see also Brain
Cerium
radioactive, 537
Chloralose
pulmonary ventilation and, 479
Chloride
gastric secretion and, 109
reabsorption and excretion of, 509
renal damage and, 510
see also Sodium chloride
Chlorine
aqueous and vitreous fluid and, 246
Cholates
bile acids and, 94
Cholesterol
absorption of, 123
atherosclerosis and, 454
deposition of, 390
fetal metabolism and, 28
in ovaries, 21
thyroid and, 57
vascular disease and, 390
Choline
renal lesions and, 451
tetraethylammonium and, 566
Cholinesterase
inhibition of, 418
in lymph, 356
in lymphoid tissue, 360
macrocytic anemia and, 341
methadon and, 579
tetraethylammonium and, 568–69
Chromosin
from thymus, 356
Chromosomes
protein in, 359
testosterone and, 366
from thymus lymphocytes, 356
Cincophen
liver and, 87
ulcer formation and, 129
Circulation
chemical agents and, 454–58
cold and, 445
in extremities, 442–45
in organs, *see* specific organs
peripheral, *see* Peripheral circulation
pregnancy and, 447–48
pulmonary reflex control of, 459
tetraethylammonium and, 565
time, 441
measurement of, 441
see also Arterial pressure, Cardiac output, Heart, and Vasomotor phenomena
Citric acid
salivary secretion and, 105
Cocaine
nerve impulse and, 182
Coenzyme I
destruction of, 420
oxygen deficiency and, 420
Cold, *see* Temperature
Colostrum
constituents of, 29–30

Connective tissue
of symphysis
relaxin and, 28–29
Copper
distribution of in chick embryo, 10
nerve membrane depolarization and, 181
Coproporphyrin
as hepatic dysfunction indicator, 93
Cornea
fibrous structure of, 245
Corpus luteum
formation of in pregnant mare, 23
Cortex, cerebral, *see* Cerebral cortex
Corticosterone
maze learning and, 292
Creatine
muscle relaxation and, 324–25
thymectomy and, 359
Creatinine
estimation of, 494
glomerular filtration and, 505
Jaffe reaction for, 494
protein intake and, 497
Crystallin
of lens, 246
Curare
brain and, 215
bronchial musculature and, 470
esophagus and, 106
hemorrhage and, 127
Cyanide
nerve depolarization and, 182
respiratory inhibition by, 11
Cytochrome-*c*
dinitrophenol and, 52
in heart muscle, 413
Cytoplasm
of lymphocytes, 359

D

DDT
brain electrical activity and, 214
Deciduomata
physiology of, 24
Defense mechanisms, see Antibodies and Antigens
Dehydrogenase
pregnancy, lactation and, 38
stilbestrol and, 52
Depeptidase
of thymus, 357–58
Desoxycorticosterone
hypertension and, 451
liver glycogen and, 65
muscle twitch tension and, 303
peptic ulcer treatment with, 129
pressor effect of, 455
Desoxycorticosterone (*cont.*)
thymic atrophy and, 364
thymic weight and, 364
Development, embryonic, 1–20
blood constituents and, 12–13
differentiation, 3
genic action in, 3
drugs on, 7
enzyme action and, 9–11
glycolysis and, 10
gonadectomy and, 14
of heart, 387–88
heat and, 7
neural crest and, 15
neural plate and, 15
nutrition and, 11–12
rate of
oxygen consumption and, 10
self neuralization, 15
sex differentiation, 14
synthesis in embryo, 7
twinning and extremity duplication, 7
viruses on, 7
vitamin deficiency and, 5–6
Diabetes
cerebral damage and, 63
estrogen therapy and, 63
insulin requirement and, 62–63
phosphatase and, 50
Dibenamine
clinical application of, 571
epinephrine action and, 569–70
heart and, 570–71
hypertension and, 570
ovulation inhibition and, 35–36, 154
sympatholytic action of, 570
Digestive system, 103–38
appetite and hunger
carbohydrates and, 103–4
mechanism for, 104
nonnutritive material and, 104
olfactory acuity and, 103
temperature and, 103
thirst, 104–5
vagotomy and, 129–30
see also individual organs
Digitalis
muscle metabolic breakdown and, 423
Digitoxin
cardiac histamine output and, 419
heart and, 420
Dihydroergocornine, 457–58
action of, 572
Dihydroergotamine
action of, 572
Diiodotyrosine
metabolism stimulation and, 55
thyroid synthesis of, 55

Di-isopropylfluorophosphate
bronchospasm and, 470–71
muscle conduction and, 309
nerve conduction and, 184–85
Dinitrophenol
metabolism stimulation by, 52
oxygen consumption and, 52–53
Dyes
heart and, 390

E

Ear
basilar membrane elasticity of, 231–32
cochlea
damping and selectivity of, 233
endolymph flow from, 234
elasticity of, 231–32
sound phase relations within, 232
electrophonic effect, 235
ossicles
movements of, 232–33
spiral organ (of Corti)
differentiation of, 233–34
projection of, 237
stria vascularis, endolymph production and, 234–35
windows of, phase difference between, 232
see also Hearing
Edema
cardiac output and, 403
cold and, 445
pulmonary, 475
Eggs
activation of
redox potentials and, 1–2
biotin deficiency in, 5–6
birefringence in, 1
cyanide sensitivity of, 10–11
impedance variations in, 561
molecular orientation in, 1
nuclear abnormalities of
nucleic acid synthesis and, 4–5
viability of, 3
water intake and, 556
Electrocardiography, *see* Heart
Electroencephalography, *see* Brain, electrical activity of
Embolism, pulmonary, 472
Embryo, *see* Development, embryonic
Emotion
brain electrical activity and, 216–17
Encephalin
properties and action of, 456
Endocrine glands
blood formation and, 343
metabolic functions of, 45–82
see also specific glands
Enterogastrone
gastric secretion and, 113–14
ulcer formation and, 128–29
Enzymes
embryonic development and, 9–11
follicular growth and, 22
formation of
genes and, 3
heart metabolism and, 412–16
liver and, 84
ovulation and, 22
substrates of, 38
see also specific enzymes
Epilepsy
convulsant drugs and, 221
electroencephalography and, 218–22
myoclonic seizures and, 211
Epinephrine, 145–50
in analgesia, 69
blood flow and, 443
blood sugar and, 69, 149–50
bronchodilator action of, 470
cortical sudanophilic material and, 150
dibenamine and, 569–70
ergot alkaloids and, 572
exercise and, 69
ganglia blockade and, 569
ganglionic transmission and, 149
glycolysis and, 49
heart and, 152–53, 392
hypertension and, 449, 455
liberation of, 148–50
lymphopenia and, 370
muscle twitch tension and, 304
norepinephrine and, 146–47
output of, 455–56
oxygen and, 69–70
from phenylalanine, 70
potentiating action of, 456
in sympathetic ganglia, 147
tetraethylammonium and, 568
thyroid and, 56
Ergotamine
pulmonary arterial pressure and, 472
Ergothioneine
as a thyroid-inhibiting agent, 60
Erythrocytes, *see* Red blood cells
Erythropoiesis, 335–45
hormones and, 343–44
pyridoxine deficiency and, 336
reviews on, 344
Esophagus
peristalsis in, 106
Estradiol
distribution of in blood, 30
feminizing effects of, 14
red blood cell permeability to, 557
spleen size and, 365
thymus and, 365

Estrogens, 30–31
accumulation of in birds, 30
areolae pigmentation and, 37
bone marrow and, 343–44
cervical mucus and, 24–25
embryonic development and, 6–7
gonadotrophic action and, 33–34
liver and, 30–31, 89–90
male accessories and, 33
metabolic pathways of, 31
Estrone
lymphoid tissue and, 365
Ether
nerve conduction and, 182
Ethyl urethane
nerve impulses and, 182
Evans blue (T 1824)
blood volume estimation and, 435–36
Exercise, *see* Muscular exercise
Eye
enucleation of, 451
innervation of, 140–41
intraocular muscles, 248
movement of
cortical areas for, 164
oculomotor and trochlear nerves and, 275
nystagmus, 250
permeability and, 559
transplantation of, 276–77
vitreous
intraocular pressure and, 246
see also Cornea, Lens, Vision, etc.

F

Fat
absorption of, 122–23
adrenal cortex and, 65
fecal excretion of, 126
gastric emptying and, 106–7
hepatitis and, 84
lipogenesis, fetal, 8
sympathetic nervous system and, 149
synthesis of
diabetes and, 62
thyroid and, 56–57
Fertilization, 1–3, 23
hormones and, 23
hyaluronidase and, 2, 31
phosphatase cytolytic action and, 1
respiratory mechanism and, 2
zona pellucida and, 23
see also Reproduction
Fibrinogen
as embryo nutriment, 11–12
Fluorescein
excretion of, 94
heart studies and, 406
Fluoroacetate
cortical rhythm and, 214
Folic acid
anemia and, 338–42
fat absorption, pancreatic juice and, 117
hyperthyroidism and, 58
lactation and, 30
liver antipernicious anemia factor and, 339–40
porphyrin production and, 336
radiation and, 533
sprue and, 338–39
tyrosine metabolism and, 341
Formaldehyde
renal damage and, 511
Frostbite
lesions in, 445
Fructose
glycogen synthesis and, 48

G

Galactose
renal absorption of, 509
Gall bladder
size decrease of, 94
Ganglia
amitotic division and, 140
blockade of
ammonium salts and, 569
epinephrine and, 569
magnesium ion and, 569
nicotine and, 569
piperidines and, 569
tetraethylammonium and, 565–66
culture maintenance of, 140
ganglionectomy
skin and, 141
Ganglia, sympathetic
epinephrine and, 147, 149
Gastrin
preparation and assay of, 113
Genes
differentiation and, 3–4
genic selection
environment and, 36
for vestigial wings, respiration and, 4
Genetics
electroencephalography and, 215–16
mutations
radiations and, 529–31
Globulin, *see* Proteins, plasma
Glucose
absorption of, 122
of blood
brain electrical activity and, 212–13
methadon and, 578
diabetes and, 61–62
embryo nutrition and, 11

Glucose (*cont.*)
red blood cell permeability and, 557
skin radiation and, 535
uptake of, 554
utilization of
adrenalectomy and, 64–65
extrahepatic tissue and, 62
insulin and, 47
Glucuronic acid
conjugates of, 494
liver and, 31
Glucuronidase
tissue proliferation and, 72
Glutamic acid
learning and, 294
Glutathione
sulfhydryl groups and, 414
Glycine
blood flow and, 443–44
pyrrole ring formation and, 335
uric acid excretion and, 509
Glycogen
glycogenesis
by heart, 48, 414
oxygen consumption and, 47
in granulocytes, 360
in ovum, 21
Glycols
glomerular filtration and, 505
Glycolysis
in embryos, 10
methadon and, 579
of spleen, 360
Glycoprotein
in ovum, 22
Glycosides
cardiac, 418–19, 421–22
Gold
lymphoid disease and, 538
Gonadotrophins
androgen production and, 34
estrogen precursor and, 34
fertility and, 36
trophoblastic and placental secretion of, 28
Gonads
pituitary gland and, 34
radiation and, 530
Growth, 71–72
endocrine influence on, 71–72
see also Development, embryonic
Growth hormone, *see* Pituitary, anterior

H

Hallochrom
reticulocytes and, 342
Headache, 168–69
Hearing, 231–44
Hearing (*cont.*)
acoustic trauma and, 235–42
cortical areas for, 237–40
deafness
congenital, 242
fenestration and, 241
hysterical and partial, 241
figure function of, 278–79
frequency selectivity and, 233
high tones
auditory nerve partial section and, 235–36
basal cell nerve coil atrophy and, 236
low tones and, 236
medial geniculate body lesions
auditory cortex and, 238
nervous mechanisms for, 237–40
pure tone duration and, 233
sound conditioning
auditory area ablation and, 239
auditory cortex ablation and, 238
colliculi destruction and, 238–39
testing of
conduction and nerve deafness and, 241
difference limen and, 240–41
in infants, 242
speech perception and, 241
tone phase changing and, 240
see also Ear
Heart, 387–434
anterior pituitary extract and, 70
arrhythmia, 390, 412
inositol and, 416
atrium
atrial pressure, 400
fetal atrial circulation, 388
location and shape of, 388
ballistocardiography, 398
bradycardia
methadon and, 577
cardioaccelerator pathways of, 142
catheterization of, 400–1
circulation time measurement of, 395–96
coronary sinus
anastomoses of, 389
coronary system of, 405
cytochrome-*c* and, 413
dibenamine and, 570–71
electrocardiography
atrioventricular bundle and, 408
calculations for, reviews on, 410
in embryonic heart, 409
explants and, 409
gases and, 410
hemorrhagic shock and, 440
injury and, 408–9
mental influences on, 410
papillary muscle and, 409
reviews on, 407–8

Heart (*cont.*)
embryonic, 387–88, 409
rhythmicity of, 394
endocrines and, 416
epinephrine sensitization and, 152–53
ergot alkaloids and, 572
eustachian valve and, 388
failure, 414
Gaskell effect and, 393
glycosides of, 418–21
infarcts of, 406
innervation of, 141–42
Kent's fibers of, 388
metabolism of, 411–23
drugs and, 416–23
glycogen storage and, 414
oxygen consumption, 415
pyruvate and, 414–15
sulfhydryl groups and, 413–14
morphology of, 387–91
muscle
adenosinetriphosphate and, 411–12
conductivity of, 395
contractility of, 391–92
excitability of, 392–93
metabolic disturbance of, 422–23
refractory period of, 394–95
rhythmicity of, 393–94
oxygen consumption and, 415
pH and, 391
precollagen fibers in, 389
pressure in, 400
Purkinje fibers of, 387
rate
blood flow, pressure and, 407
nerve stimulation and, 142
venous pressure and, 405
renal function and, 503
size of, 390–91
sympathomimetic substance and, 417
Taussig heart, 389
tetraethylammonium and, 565
tricuspid valve surgery, 389
valves of, 389
venous pressure and, 401
vitamin E and, 415
see also Cardiac output
Hematin
renal function and, 518
Hematopoiesis, *see* Blood, hematopoiesis
Hematuria
renal damage and, 513–14
Heme
synthesis of, 335–36
Hemoglobin, 513–20
administration of, 518
as blood substitute, 518
dried
preparation of, 519
of embryos, 13
Hemoglobin (*cont.*)
fetal, 13
hemorrhagic shock and, 519
oxygen capacity of, 477
oxygen diffusion and, 476
oxyhemoglobin
dissociation curve of, 477
preparation of, 518–19
protoporphyrin and, 336–37
respiratory alkalosis and, 478
stercobilin and, 93
Hemorrhage, 437–41
blood volume and, 440
infusion fluids and, 440
renal circulation and, 439
shock and, 437
Heparin
fat absorption and, 123–24
peptone shock and, 441
Hexaethyl tetraphosphate
action of, 457
Hexestrol
excretion of, 31
Histaminase
gastric secretion and, 111
Histamine
enterogastrone and, 113–14
of gastric juice, 112
leukemia and, 360
radiation and, 533–34
in sympathetic nerves, 146
ulceration and, 127
Histidine
heart rate and, 417
Histone
of thymus, 358
Hormones, *see* specific hormones and individual endocrine glands
Hyaluronidase
fertilization and, 31
as a follicle cell disperser, 2
germinal epithelium and, 32
maximum activity level of, 53
myxedema and, 53
source of, 2
of sperm, 32
Hydrochloric acid
achlorhydria, 110
formation of, 108–9
gastric acidity and, 558–59
gastric mucosa output of, 109
riboflavin and, 115
ulcer production and, 127
Hypertensin
hypertension and, 449
purification and properties of, 455
Hypertension
argyrophillic substances and, 389–90
dibenamine and, 570
endocrine, 451–52

Hypertension (*cont.*)
experimental, 449–52
hepatic blood flow and, 442
hypertensinase, 450
nephrectomy and, 453
neurohypertension, 450–51
neurohypophysis and, 453–54
pregnancy and, 27
sympathectomy and, 452
tetraethylammonium and, 566
typhoid vaccine and, 453
vasoexcitor material and, 449–50
Hypophysis, *see* Pituitary
Hypotension
methadon and, 577
merperidine and, 577
pentaquine and, 573
Hypothalamus
anoxia and, 154
sleep and, 155
sympathetic activation and, 154

I

Ileum, *see* Intestine, small
Immersion foot, 445
Inositol
arrhythmia and, 416
Insulin, 45–49
action mechanism of, 46
blood amino acids and, 63–64
diet and, 64
embryonic development and, 6
gastric motility, vagotomy and, 107
glycogenesis and, 47–48
glycogenolytic factor in, 48–49
hexokinase reaction and, 46
liver fat and, 88
thiamine and, 63
vitamin C and, 63
Intestine
methadon and, 577
phosphatase and, 49–50
radiation and, 536
tetraethylammonium and, 567
Intestine, large
colon, 125–26
gases and, 125–26
Intestine, small, 118–25
absorption in
resection and, 125
duodenum
pressure waves in, 106
ileum
tetraethylammonium and, 567
innervation of, 143–44
reflexes and, 143–44
motility of, 118–19, 144
pendulum movement and, 119
stimuli and, 118
Intestine (*cont.*)
secretion of, 119–25
goblet cells and, 120
hypoglycemia action and, 120
lavage and, 119–20
visceral sensation and reflexes, 125
Inulin
glomerular filtration and, 504
Iodine
diiodotyrosine synthesis inhibition by, 55
distribution of, 53–54, 110
goiter and, 55–56
Graves' disease and, 538
metabolism of
thyroid and, 54–55
Iodoacetamide
nerve depolarization and, 182
Ions
nerve membrane depolarization and, 179
permeability of, 560–61
Iron
absorption of, 120–21
adrenal glands and, 345
in blood, 497
fetal
source of, 27
hemochromatosis and, 120
mesenteric lymphatics and, 355
metabolism of, 344–45
intestinal mucosa and, 344
plasma globulin and, 345
toxicity of, 121
Ischemia, renal, 512–13
Isoamidone
analgesic properties of, 574
Isomethadon
analgesic potency of, 575
Isotopes
laboratory use of, 527–28
see also Radiation

J

Joints
sensibility of, 168

K

Ketogenesis
hormones and, 68–69
Kidney, 455, 493–526
abdominal pressure and, 446
acid-base balance and, 507–8
anuria, 515
arteriovenous shunts in, 496
blood flow in, 500–4
cold pressor test and, 497–98
exercise and, 497

Kidney (*cont.*)
crush syndrome and, 440
damage of
glomerular filtration and, 505–6
hemoglobin and, 513–20
induction of, 509–12
treatment of, 512
dibenamine and, 571
diuresis
hypothalamus and, 155
function of
abdominal pressure and, 504
development of, 498–500
glomerular damage, 510
glomerular development, 499
glomerular filtration, 504–6
cold pressor test and, 497–98
exercise and, 497
hypertension and, 451–53
innervation of, 496
ischemia and, 512–13
lesions of, 496
nephrotoxins, 516
phosphatase estimation of, 495
pressor substances
renin
determination of, 453
hypertension and, 449–50
lymph flow and, 355–56
pressor substances and, 450
see also Hypertension
pressure breathing and, 498
renal insufficiency estimation, 495
shock and, 438
tubular activity of, 506–9
see also Creatinine, Urea, etc.

L

Lactation, 29–30
purified diets and, 30
reviews on, 29
Lactones
heart and, 416
Lactose
food selection and, 103
Lens
accommodation and, 248
fluorescence in, 246
Leucine
thymic atrophy and, 362
Leukemia, *see* Leukocytes, leukemia
Leukocytes
count
radiation and, 533
leukemia
cysteine and, 362
lysine and, 362
protein synthesis and, 359
radioactive isotopes and, 538
Leukocytes (*cont.*)
leukemia (*cont.*)
spleen histamine and, 360
thymectomy and, 358
urethane and, 368
lymphocytes, 369–73
antibody formation and, 376–78
blood
level of, 369–73
lymphopenia, 370–73
spleen and, 370–71
chromosomes of, 356–57
irradiation and, 534
lymphocytolysis, 364
bacteria and, 368
tuberculoprotein and, 368
physical stimuli and, 369–70
pituitary-adrenal secretion and, 363
radiation and, 367
Light
light adaptation, 255–56
light sense
vision and, 253–56
Lipase
gastric emptying and, 107
Lipids
adrenal cortical, depletion of, 150
in lymphoid tissue, 360–61, 366
Lipine
heart and, 417
Lithium chloride
myosin fibrillar structure and, 7
Liver, 83–102
adrenal cortex and, 66
antibody formation and, 379
antidiuretic substances and, 90
arteriovenous pathways of, 448
ascites and, 90–91
blood flow in
cirrhosis and, 442
estimation of, 92, 442
pregnancy and, 442
pyrogens and, 442
circulation of, 91–92
cirrhosis
reversibility of, 86–87
estrogen inactivation and, 30
estrogenic physiology and, 89–90
fatty
lipotropic factor and, 87
pancreatic extracts and, 117
thyroidectomy and, 56
hepatectomy, 88–89
restoration rates and, 89
injury, 83, 85–90
chemical agents and, 85–87
diet and, 87–88
methionine and, 84–85
mitotic rates in, 88
nutrition and, 84–85

Liver (*cont.*)
parenchymal damage of
tests for, 83
phosphatase and, 89
regeneration of, 88–89
reviews on, 83
shock and, 92, 438
vasodilator material and, 439
viral disease and, 87
yttrium and, 537
Lixose
in heart, 416
Lungs
alveolar pressure, 470
anastomoses of, 471
arteriovenous anastomoses and, 448
asthma and, 471
breathing efficiency and, 470
circulation of, 152, 460, 471–72
distensibility of, 469–70
drowning and, 470
function measurement of, 484
intrathoracic pressure, 470
lobes of
arterial flow and, 469
lymphatics of
absorption through, 355
pressure breathing, 473–75
edema and, 475
extremity blood flow and, 442–43
pulmonary edema
bilateral vagotomy and, 152
pulmonary emboli
electrocardiographic changes and, 152
stellate block and, 152
pulmonary vessels
pressure and, 152
stretch receptors, 480–81
vasoconstriction of, 473
see also Respiration
Lymph
circulation and composition of, 355–56
in lungs, 473
Lymphatic system, 355–86
lymphoid tissue
composition and metabolism of, 359–61
extracts of, 357
globulin production and, 373–75
hyperplasia and, 363–64
hypertrophy of, 358
lipids in, 360–61, 366
nitrogen and sulfur mustards and, 367
protein metabolism and, 66
radiant energy and, 366–67
size and structure of
age and, 362–63
growth hormones and, 366
nutrition and, 361–62
Lymphatic system (*cont.*)
lymphoid tissue (*cont.*)
pituitary-adrenal secretion and, 363–65
sex hormones and, 365–66
Lymph nodes
age changes in, 362
origin of, 362

M

Macrophages
antibody formation and, 378
Magnesium
polypnea and, 483
seizures and, 286
Mammary glands, 29
proliferation of, 29
see also Lactation
Mannitol
determination of, 494
inulin clearance and, 505
Medulla oblongata
pressor regions of, 153
vagal respiratory reflexes and, 482
Membranes
concentration potentials and, 553
diffusion of, 551
distribution across, 552
electrical potentials in, 548–49
of red blood cells, 556
see also Permeability
Menopause
hypertension and, 453
Menstruation
coiled arterioles and, 24
phosphatase and, 24
threshold bleeding and hormones, 25
Merperidine
anesthetic properties of, 578
gastrointestinal and genitourinary action of, 577–78
hypotension and, 577
intestinal constipation and, 577
metabolism and, 578–79
Metabolism
immobilization and, 71
permeability and, 554
see also organs and specific substances
Methadon
activity of
nuclear changes and, 575
anesthetic properties of, 578
cardiovascular action of, 577
D- and L-forms of, 573–74
gastrointestinal and genitourinary action of, 577–78
hyperglycemia and, 578
metabolism and, 578–79
as morphine substitute, 580

Methadon (*cont.*)
nervous system and, 576
pain and, 574
tolerance to, 579–80
toxicity of, 579
Methemoglobin
renal injury and, 440
Methionine
liver damage and, 84–85
renal reabsorption of, 508–9
Methylcholanthrene
hereditary dwarfism and, 4
Methylscopalamine
gastric secretion and, 111
Metrazol
epilepsy and, 221
Morphine
gastric secretion and, 111
pancreatic secretion and, 116
substitutes for, 580
Mucin
secretion and action of, 113
Muscle, skeletal, 297–334
adenosinetriphosphate and, 411–12
blood vessel dilation in, 445
bioelectric potentials in, 173–98, 307–10
cardiac, *see* Heart
conduction of
acetylcholine and, 309
contraction of
actomyosin and, 316
adenosinetriphosphatase and, 314, 324–25
energy change in, 319–20, 322
entropy and, 321–22
potassium and, 304–5
resting tension and, 321
tension generation and, 322
thermodynamic reversibility of, 307
crossing of
nerves and, 276
derivation of, 15
differentiation of, 9–10
elasticity of, 305–6
excitation of, 308–9
extraocular, 140–41, 248
fiber
structure of, 299
human
mechanics of, 302
intestinal stimuli and, 144
latency relaxation in, 300–2
length-tension relation of, 300
mechanical changes of, recording of, 298–99
mechanical coupling and, 299
mechanochemistry of, 310–11
membrane potential of, 176
contraction and, 309–10
potassium and, 307–8
Muscle (*cont.*)
membrane potential of (*cont.*)
stretch and, 308
motor cortex and, 163–64
myelinated nerve fibers of, 195
myothermy, 206–7
myxedema and, 305
permeability of, 557
reviews on, 297
post-tetanic potentiation of, 303–5
recovery coupling in, 323–26
resting tension of, 300–1
reviews on, 327
shock, 440
tetanus tension and, 302
tetraethylammonium and, 566
ultrastructure of, 311–14
Muscular exercise
epinephrine and, 69
respiration and, 480
Mutations, *see* Genetics
Myosin
adenosinetriphosphatase and, 2, 314–15
in cardiac muscle, 422
in egg, 2
extraction of, 312–13
muscle fatigue and, 313

N

Narcotics
on axons and synapses, 194
Neostigmine
tetraethylammonium and, 568
Nerve
axon
anelectrotonic potential in, 178
electrotonic change and, 178
injury to, excitability and, 192
oscillation in, 178
bioelectric potentials in, 173–98
conduction in
chemical transmission of, 139
cholinesterase and, 184–85
electrolytes and, 179–81, 188
membrane potential and, 179
denervation
escape mechanism and, 151
electrotonic potentials of, 176–77
excitation of
anesthetic agents and, 181–82
metabolic inhibitors and, 182
organic anions and, 183
sugars and, 183
thiamine chloride and, 183
triturus toxin and, 183
fibers of
ascending and descending currents on, 190

Nerve (*cont.*)
fibers of (*cont.*)
blocking temperature and, 187
C fibers, 179
potassium, temperature and, 188
potentials of, temperature and, 187–88
rheobasic strength currents and, 179
heat block establishment and, 186–87
invertebrate synapses, 194–95
membrane potential of, 173–76
Donnan equilibria and, 175
electromotive force of, 175–76
fractions of, 176–77
ions and, 177–78
lowered temperature and, 186
oxygen and, 174–75
polarization asymmetries and, 177
potassium and, 174
muscle and, 195, 276
norepinephrine and, 146
from periventricular region, 143
permeability and, 559
spike potential and, 178–79
stimulation of
respiratory center and, 482
synaptic and axonal conduction, 193
thyroid and, 59
Nerves
auditory
function of, 235–37
carotid sinus
electrical stimulation of, 459
of heart, 388–89
hypogastric
fibers in, 144
ocular, 140–41
oculomotor
eye movements and, 275
optic
blood supply of, 247
crossing of, 277
nutrition and, 247
physiology of, 251
phrenic
afferent fibers of, 143
pain transmission in, 143
respiration and, 482
splanchnic
efferent impulses in, 144
sympathetic, *see* Sympathetic nervous sytem
trochlear
eye movements and, 275
Nervous system, central
bioelectric potentials in, 173
cortical transection
motor coordination and, 274
dibenamine and, 571
Nervous system, central (*cont.*)
frontal area destruction
memory and, 270–71
frontal lobe function, 272–73
methadon and, 576
Porteus Maze Test
psychosurgery and, 272
reorganization of
review on, 275
reverberating circuits and, 278–79
rhythmicity and, 191
social behavior and, 271–72
somatic functions of, 161–72
structure of
behavior and, 277–78
synaptic potentials, 188–89
visceral functions of, 139–60
see also Brain, Cerebellum, Cerebral cortex, etc.
Neural crest
development and, 140
excision of, 16
pigment production and, 15–16
thoracolumbar system and, 140
Neurohypophysis
hypertension and, 453–54
innervation of, 35
Neurons
of dorsal roots, 145
intramedullary conduction properties of, 193
motor
reduction of, 16
neuron somata
action potential of, 193
configuration of, 192–93
impulse velocity and, 193
phrenic
respiration and, 482
Nicotine
circulation and, 458
ganglia blockade and, 569
reflex discharge and, 194
Nicotinic acid
absorption of, 124
embryonic development and, 5
embryonic synthesis of, 7–8
Nitrates
arterial pressure and, 457
Nitrogen
elimination of
oxygen and, 476–77
of lymphoid tissue, 361
Nitrogen mustards
anamnestic response and, 376
cellular metabolism and, 2
glycolysis and, 360
lymphoid tissue and, 367
nucleic acid synthesis and, 8

Nitrogen mustards (*cont.*)
pituitary-adrenal cortical secretion and, 367–68
serum protein and, 374–75
Norepinephrine, 145–48
dibenamine and, 570
inhibitory action of, 571
properties of, 147
sympathin and, 146–47, 456–57
sympathomimetic substance and, 145–46
Novocaine
muscle depolarization and, 309
Nucleic acids
as differentiation mechanisms, 4
embryo synthesis of, 8–9
irradiation and, 528
in lymphocyte cytoplasm, 359
thymus, 356–57
turnover of, 358
Nucleoproteins
from thymus, 356–57
Nutrition
diet selection, 289
embryonic, 11–12
lymphoid tissue and, 361
sensory nerve and, 247

O

Obesity
hypothalamic lesions and, 154
vagotomy and, 154
Ouabain
heart and, 418
oxygen uptake and, 419–20
Ovary
connective tissue of, 22
graffian follicle muscle, 22
histochemistry of, 21
hyperemia of
gonadotrophin and, 34–35
pituitary function and, 34
spiral artery of, 447–48
transplants of, 23
Ovulation
enzymes and, 22
gonadotrophins and, 35
hypophysis and, 154
Ovum
development of, 21
in eye and abdominal cavities, 12
transport of, 26
Oxalate
renal damage and, 510
Oxidase
in embryo, 413
Oxidation
egg activation and, 1–2
Oxygen
alveolar, 475–76
breathing of, 480
bone marrow and, 346
consumption
cardiac output and, 415
coronary flow and, 407
histone and, 358
membrane potential and, 176
methadon and, 579
diffusion of, 476
heart muscle uptake of, 419
hemoglobin and, 477
intestinal motility and, 118–19
oxidative metabolism
membrane potential and, 174–75
steroacuity and, 257
Oxygen deficiency
brain electrical activity and, 213
capillary permeability and, 439
coenzyme I and, 420
epileptic activity and, 221–22
epinephrine liberation and, 148
heart and, 393, 395
hormones and, 343
intestinal motility and, 118
lung volume and, 479–80
maze retention and, 291
performance and, 290
postsynaptic neurons and, 193–94
respiration and, 479–80
systolic arterial pressure and, 459
tissue, 478
Oxygen tension
alveolar-arterial difference in, 476
of blood, 478

P

Pain
headache, 168–69
hyperpathia, 169
methadon and, 574
types of, 574
Pamaquine
sympathetic reflexes and, 573
Pancreas, 115–18
acinous cells of, 115–16
antifatty liver factor of, 87
carbohydrate metabolism and, 61–64
enzymes of, 116
gastric juice and, 116
vagotomy and, 116
fibrocystic disease of, 117–18
fistula of, 115
islets of, 61–62
lipodieresis and, 117
necrosis induction in, 117
secretion of
duodenal pH and, 116

Pancreas (*cont.*)
starvation and, 62
Pancreozmin
action of, 116
Parathyroid gland
light and, 73
phosphate metabolism and, 72–73
Parturition
in opposum, 27
Penicillin
absorption of, 124
renal clearance of, 503
renal damage and, 511–12
sperm viability and, 32–33
Pentaquine
hypotension and, 573
nervous system and, 457
sympathetic reflexes and, 573
Pentobarbital
carotid sinus reflex and, 145
gastric emptying and, 107
Pentothal
brain electrical activity and, 213
Pepsin
ulcer formation and, 127
nitrogen compounds and, 113
Peptidase
in lymphocytes, 360
Peripheral circulation, 435–68
see also Arterial pressure, Capillaries, Vasomotor phenomena, etc.
Permeability, 545–64
bioelectrics and, 560
definition of, 547–48
diffusion, 551
driving forces of, 548–51
electrochemistry and, 553
of eye, 559
impedance measurement and, 561
ionic accumulation and, 554
metabolism and, 554
of muscles, 557
radiophosphorus and, 553
stomach and, 557–59
surface phenomena and, 552–53
see also Membranes
Pharmacology, 565–86
of autonomic nervous system, 565–73
see also specific substances
Phenylalanine
thymic atrophy and, 362
Phenylhydrazine
blood volume estimation and, 436
plasmal and, 21
Phloridzin
nerve potential and, 182
renal tubules and, 509
Phosgene
respiration and, 480–81
Phosphatases, 49–52
Phosphatases (*cont.*)
adrenalectomy and, 50
castration and, 50
diabetes and, 50
fertilization and, 1
glucose and, 49
hypophysectomy and, 50–51
of intestine, 123
in kidney, 455, 495
liver and, 89, 356
during menstrual cycle, 24
in ovarian tissues, 38
of pancreas, 116
phlorhizinization and, 49
in pituitary gland, 33
during pregnancy, 51
salivary glands and, 105
in uterus, 25–26
Phosphates
parathyroids and, 72–73
superior cervical ganglion and, 194
Phosphocreatine
digitoxin and, 420
heart and, 411–12, 420
insulin and, 48
Phospholipids
absorption of, 123
fetal synthesis of, 8, 28
Phosphorus
lymphoma and, 537
placenta permeability to, 560
radioactive
plant growth and, 536
therapeutic use of, 538
Physostigmine
adrenal medulla and, 149
cardiac muscle refractory period and, 394–95
Pigments
in eye, 250
metabolism of, 92–93
see also individual pigments
Pilocarpine
salivary secretion and, 105
Piperidines
analgesic activity of, 575–76
ganglia blockade and, 569
Pituitary
embryonic growth and, 14
gonads and, 34
hypophysectomy and, 33
hypothalamus and, 155
luteinizing hormone and, 154
radiation and, 366–67
see also Gonadotrophins
Pituitary, anterior, 70–71
adipokinetic activity and, 70
adrenal cortex and, 68–69
adrenotrophic hormone
adrenal cortex and, 68

Pituitary, anterior (*cont.*)
adrenotrophic hormone (*cont.*)
anamnestic response and, 375–76
blood globulins and, 373–75
blood lymphocytes and, 369–73
lymphoid tissue and, 363–65
extract of
hexokinase reaction and, 45–46
oxygen consumption, cardiac output and, 70
growth hormone of
lymphoid tissue and, 366
histochemistry of, 33
renal damage and, 511
Pituitary, posterior
antidiuretic hormone of, 499
Placenta, 27–28
ascorbic acid in, 8
permeability of, 27–28, 560
viable
fetal death and, 26–27
Plasma
hepatectomy and, 89
plasma cells
antibody formation and, 378
Platelets, blood
count of
radiation and, 533
spleen and, 360
Poliomyelitis
vasomotor disturbances in, 444
Polynucleotide
bone marrow cell and, 347
Porphyrin
metabolism of
reviews on, 335
Porphyrinuria
casein and, 93
Posture
arterial pressure and, 449
Potassium
actomyosin and, 316–17
electrocardiography and, 409
excretion of, 506–7
in fetal erythrocytes, 13
intestinal muscle and, 150–51
membrane potential and, 174–75, 307–8
muscle contraction and, 303–4
muscle permeability to, 557
osteoporosis and, 453
of red blood cells, 13, 556
Pregnancy, 26–27
arterial pressure and, 451–52
cold pressor tests and, 453
hepatic blood flow and, 442
iodine determinations in, 53
phosphatase during, 51
ovarian hyperemia test for, 34–35
respiration and, 479
Pregnancy (*cont.*)
tests in amphibia, 35
vascular system in, 447–48
Pregnanediol
excretion of
pregnancy and, 27
Pregnenalone
performance and, 292–93
Progesterone
corpus luteum and, 23–24
fertilization and, 23
respiration and, 479
Propylamines
pressor activity of, 456
Proteins
absorption of, 122
adrenocorticotropin and, 69
gastric emptying time and, 107
hypertension and, 450
liver and
reviews on, 83–84
liver fatty infiltration and, 87–88
in lymphocyte chromosomes, 359
metabolism of
adrenal cortex and, 65–66
thyroid control of, 58
in milk and colostrum, 30
of muscle, 311–12
electrophoresis of, 313
synthesis of
growth and, 72
phosphate bond energy in, 72
turnover rate of
adrenalectomy and, 375
urea and creatinine concentrations and, 497
Proteins, plasma
albumin
renal function and, 502
of embryo, 12
globulin, 373–74
Ac globulin, 441
adrenals and, 373–75
hypertension and, 450
irradiation and, 534
Protoporphyrin
synthesis of, 335
Psychology, physiological, 269–96
behavior
nervous system and, 270–79
diet and, 293
drugs and, 291–93
electroconvulsive shock and, 279–83
motivation and, 286–91
seizures
conflict and, 284–85
diet and, 286
stimulation repetition and, 284
reviews on, 269–70
Pteroylglutamic acid, *see* Folic acid

Pyribenzamine
salivary secretion and, 105
Pyridine
hepatic injury and, 87
Pyridoxine
antibody formation and, 377
lymphosarcoma and, 361
protoporphyrin synthesis and, 336
Pyruvate
oxidation of
heart and, 414–15
stomach and, 108

Q

Quinacrine
brain electrical activity and, 214
Quinidine
heart oxygen uptake and, 416
Quinine
absorption of, 124
on urodele embryos, 7

R

Radiation, 527–44
action mechanism of, 528–30
blood and, 532–34
internal, 536–39
reviews on, 539
skin and, 535
whole body, 530–32
see also specific types of radiation
Radiation, x-ray
lymphocytes and, 367
pituitary-adrenal secretion and, 366–67
serum protein and, 374–75
Red blood cells
anion permeability of, 557
cation permeability of, 556
erythropoiesis stimulation and, 347–48
formation of, 347
nonelectrolyte permeability of, 554, 557
permeability of, 560
radiation and, 533
volume changes and, 554
see also Erythropoiesis
Reflexes
medulla oblongata and, 482
of respiration, 482
sympathetic, 573
vagopressor
endocrines and, 454–55
vasomotor, 567–68
Relaxin, 28–29
Renin, *see* Kidney, pressor substances
Reproduction, 21–44
animal breeding and ecology, 36–37
castration and development, 26
Reproduction (*cont.*)
in females, 24–26
fetal survival, 36
in males, 31–33
reviews on, 38
spreading factors and, 38
see also Ovary, Ovulation, Spermatozoa, Testes, etc.
Respiration, 469–92
acceleration
forms of, 481
alkalosis, 478
centers of
activation of, 483
alkali and, 479
chemoceptors and, 482
electrical stimulation of, 483
inhibition of, 483
motoneurons and, 482–83
orbital cortex stimulation and, 483
paralysis of, 483
reactions of, 483
chemical regulation of, 479–80
diffusion, 478
embryo development and, 10
gas exchange and, 475–78, 484
hypopnea, 480
labyrinthine stimuli and, 483
methadon and, 576
muscular exercise and, 480
phosgene inhalation and, 480–81
polypnea, 481
postural reactions of, 481
pulmonary stretch receptors and, 480–81
pulmonary vascular fibres and, 481
rate, 483
reflexes of
medulla oblongata and, 482
phrenic nerve and, 482
reviews on, 469, 484
tetraethylammonium and, 566
thermal polypnea, 483
tracheal occlusion and, 482
venous return and, 152
ventilation
carbon dioxide and, 479
see also Lungs
Reticulocytes
ripening of
liver extract and, 342
pituitary, thyroid and, 343
Retina
day vision and, 247
of fish, 247
fovea
foveal cones, 247
tritanopia in, 258
growth-regulating factors and, 277
ora serrata of, 247

Retina (*cont.*)
refractive index of
dark adaptation and, 247
vessels of, 247
Rhodopsin
vision and, 250
Riboflavin
circulation time measurement and, 441
Ribonuclease
cytoplasmic basophilia and, 360
Ribose compounds
in genic action, 3–4
Rutin
radiation damage and, 533

S

Saliva, 105
Salivary glands, 104
sympathetic nerves in, 142–43
Sarcoma, *see* Tumors
Scurvy, 458
Sebaceous glands
hormones and, 37
Secretin
molecular analysis of, 117
pancreas and, 116
pancreatic fibrocystic disease and, 117–18
Semen
hyaluronidase in, 2
Shock, 437–41
burn, 439
cardiac output and, 437
coronary flow and, 407
crush syndrome, 440
hemorrhage and, 437
renal blood flow and, 501
vasoexcitor material and, 438
Shock, electroconvulsive, 279–83
daily activity and, 279
grand and petit mal seizures and, 280–81
habit and, 282
learning and, 280, 282–83
maze behavior and, 279–81
memory and, 283
Silica
in lungs, 470
Skin
circulation in, 443
innervation of, 141
permeability of, 560
radiation and, 535
Sodium
aqueous and vitreous fluid and, 246
in heart muscle, 419
leukopenia and, 537
muscle permeability and, 557
Sodium (*cont.*)
nerve impulse and, 179
placenta permeability to, 28
reabsorption and excretion of, 509
salts
heart rhythm and, 416
Sodium chloride
adrenalectomy and, 65
cardiac output and, 397
hypertension and, 451
Spermatozoa
antibiotics and, 32
hyaluronidase and, 32
motility of, 2
pH and, 32
water irradiation and, 528
zona pellucida penetration by, 22
Spinal cord
currents direction and, 190–91
electrical activity of, 191–92
lesions of
urinary bladder and, 153
Spleen
age changes in, 362
arteriovenous anastomoses and, 448
blood lymphocytes and, 371–72
bone marrow and, 348
desoxypyridoxine and, 362
glycolysis of, 360
steroid fractions from, 360
weight of, 362–63, 365
starvation and, 361
Sprue
fat absorption and, 122–23
pteroylglutamic acid and, 338–39
Stercobilin
origin of, 93
Steroids
glucose oxidation inhibition and, 52
glycogenic activity of, 495
heart and, 416
ketosteroids
adrenal cortex and, 67–68
see also specific substances
Stilbestrol
excretion of, 31
oviduct development and, 14
pregnanediol excretion and, 27
spleen size and, 365
Stomach
antianemic factor in, 115
gastrectomy
appetite and, 104
gastric mucosa
acidity of, 557–58
oxidative metabolism of, 108
pressure waves in, 106
secretion of
antacids and, 111

Stomach (*cont.*)
secretion of (*cont.*)
atropine and, 111
caffeine and, 115
calcium and, 111–12
chloride and, 109
diathermy and, 110
histaminase and, 111
methylscopalamine and, 111
morphine and, 111
urogastrone and, 114
Streptomycin
sperm viability and, 32–33
Strontium
fetal development and, 538
in skeleton, 537
Strophanthin
heart and, 420
Succinoxidase
stilbestrol and, 52
Sulfadiazine
on urodele embryos, 7
Sulfa drugs
absorption of, 124
sperm viability and, 32
Sulfhydryl
actomyosin and, 313, 322
adenosinetriphosphatase and, 316
Sulfur mustards
lymphoid tissue and, 367
pituitary-adrenal secretion and, 367–68
Sympathetic nervous system
fat mobilization and, 149
sympathectomy
hypertension and, 452
sympathetic reflexes
pamaquine and, 573
pentaquine and, 573
Sympathin, 457
nature of, 148
norepinephrine and, 146–47, 572
see also Epinephrine and Norepinephrine
Symphysis
relaxin action in, 28

T

Teeth
membrane vascularity and, 459
Temperature
acetylcholine and, 459
actomyosin and, 318–19
appetite, hunger and, 103
blood flow and, 444
brain and, 459
cold
blood flow and, 455
vascular disorders and, 445
cortical lipids and, 67
Temperature (*cont.*)
diathermy
gastric secretion and, 110
renal blood flow and, 451
embryonic development and, 7
intestinal sensitivity to, 144
intestine, drugs and, 151
myothermy, 306–7
nerve fiber and, 186
polypnea and, 483
radiation damage and, 529
red blood cell cation permeability and, 556–57
renal ischemia and, 512–13
ulceration and, 126
Testes
cryptorchidism
lymphatic tissue and, 365
innervation and, 143
Testosterone, *see* Androgens
Tetraethylammonium
action of, 565–69
excretion of, 569
gastric secretion and, 111
intestinal motility and, 119
sympathectomy and, 452
vasodilatation and, 566–67
Thalamus
cerebral cortex and, 161–62, 278
Thiamine
acetylcholine, heart and, 418
adrenal cortex and, 67
circulation time measurement with, 441
glucose absorption and, 122
performance and, 293
thymic involution and, 362
Thiocyanate
myosin fibrillar structure and, 7
Thiosulfate
glomerular filtration and, 504–5
Thiouracil
methylthiouracil, 61
thyroid depression and, 60
thyrotoxicosis and, 60–61
Thiourea
thyroid adenomata and, 60–61
as thyroid inhibitor, 59–60
Thymus, 356–59
antibody formation and, 377, 379
atrophy of, 362
desoxycorticosterone acetate and, 364
estradiol propionate and, 365
extract of
effects of, 358
involution of
adrenal glands and, 362
age and, 363
aminothiazole and, 368
hormones and, 364
thiamine and, 362

Thymus (*cont.*)
physiological role of, 358–59
proteins of, 356–58
thymectomy, 358–59
weight of, 363
Thyroid gland, 53–61
antithyroid agents
evaluation of, 59
energy metabolism and, 56–59
hormone
heart and, 416
hyperplasia, 358
hyperthyroidism, 58–59
inhibition of, 59–61
inhibitors on chick embryo, 6
iodide fixation and, 54
iodine determination and, 53
protein metabolism and, 58
radioactivity uptake by, 61
radioiodine and, 61, 538
vitamin A and, 57–58
Thyroxine
activity of, 54
plasma protein-bound iodine and, 53–54
synthetic
activity of, 54
Tocopherol
hepatic necrosis and, 88
Tridione
brain and, 215
Tumors
cerebral location of, 217
lymphoid, 368
lymphosacroma
hormones and, 365
pyridoxine and, 361–62
radioactive isotopes and, 537–38
radiation and, 535
Typhus fever
kidney blood flow and, 501–2
Tyrosine
pteroylglutamic acid and, 341
reticulocyte ripening and, 342

U

Ulcer, peptic
formation of, 126–29
gastric artery ligation and, 127–28
peptic activity, pyloric ligation and, 128
thermal irritation and, 126
vagotomy and, 129–30
hypothalamic hematoma and, 154
tetraethylammonium and, 567
Urea
clearance of, 502
pressure breathing and, 498
determination of, 495
excretion of, urine volume and, 508
Urea (*cont.*)
protein intake and, 497
Urease
in gastric juice, 115
Ureter
ligation of, 513
merperidine and, 578
methadon and, 578
tetraethylammonium and, 567
Urethane
lymphoid tissue and, 368
lymphopenia and, 371
Uric acid
determination of, 495
hyperuricemia induction, 495–96
Urine
determination of compounds in, 493
epinephrine and, 456
protein estimation in, 495
sulfate estimation in, 495
Urobilin
in fistula bile, 94
Urobilinogens
liver and, 93
Urogastrone
gastric secretion and, 114
Uropepsin
output of, 114
Uterus
cervix of
gradient in, 26
histochemistry of, 25–26
intrauterine pressure in labor, 27
methadon and, 577
Uvea
innervation of, 246
iris vasoconstrictors, 246
veins of
diffusion and, 246

V

van den Bergh reaction, 93
Vascularin
properties of, 457
Vasomotor phenomena
vasoconstriction
dibenamine and, 570
of lungs, 473
pressure breathing and, 474
tetraethylammonium and, 568
vasodilatation
tetraethylammonium and, 566–67
vasomotor reflex
tetraethylammonium and, 567–68
Veins, 446
gravity and, 447
of heart, 405
jugular pulse, 446
lymphopenia and, 372
uveal, 246

Veins (*cont.*)
venous plexuses, 446
Venous pressure
edema and, 445
cardiac output and, 398–99
Veratrine
carotid sinuses and, 406
muscle threshold and, 308
nerve depolarization by, 182–83
Veratrum
heart and, 416
Viruses
teratogenic effects of on embryo, 7
Vision, 245–68
accommodation and, 248
angle acuity and, 255–56
astigmatism, 249
blinking, fatigue and, 259
color vision, 258–59
dichromasy, 258
indirect adaptation and, 259
mechanism of, 258–59
trichromatic theory and, 259
cortical areas for, 164, 260
coupling and, 260
depth acuity and, 257
dioptrics and, 249
electric responses and, 250–51
electroretinogram, 252
eye transplantation and, 276–77
figure function of, 278–79
growth-regulation factors and, 277
integrating mechanisms, 260
light adaptation and, 255–56
light sense and, 253–56
limulus receptors and, 251
motion and, 256
nervous system and, 260
night myopia, 249
nonphotic stimulation and, 252
ocular tension and, 246
pigments and, 250
pupillary reflexes and, 248
reading illumination and, 259–60
refraction and, 249
reviews on, 245
space sense and, 257
threshold variants and, 253–54
visual cortex, 260
see also Eye
Vitamins
deficiency of
antibody formation and, 378
fat soluble
bile and, 94
seizure frequency and, 286
Vitamin A
absorption of, 124
carotene conversion to
thyroid gland and, 57
Vitamin A (*cont.*)
deficiency of
embryonic development and, 5
destruction of, 115
retinenes from, 250
thyroid function and, 57–58
visual sensitization and, 252
visual threshold and, 253
Vitamin A_2
color vision and, 250
Vitamin B
food selection and, 103
hepatic function and, 88
hyperthyroidism and, 59
liver inactivated estrone and, 90
renal damage and, 510
see also Ascorbic acid
Vitamin B_1
heart pyruvate and, 415
sensory nerve and, 247
Vitamin B_2
visual threshold and, 253
Vitamin B_{12}
anemia and, 337–38
Vitamin C
pancreatic insulin content and, 63
Vitamin D
absorption and, 120
embryonic development and, 5
Vitamin E
arteritis and, 458
heart and, 415

W

Water
absorption of
intestine and, 120
bound, 556
diuresis, *see* Kidney, diuresis
hoarding of, 287–88
intake of, 286–87
irradiation of, 528
retention of
DOCA and, 66
secretion of, 108–9
transfer of, 550–51, 555–56
water balance, 90–91
White blood cells, *see* Leukocytes

X

Xanthine
reticulocyte ripening and, 342
X-radiation, *see* Radiation, x-ray
Xylidine
liver damage and, 85

Z

Zymogen
salivary glands and, 105